

The American Journal of Cardiology[®]

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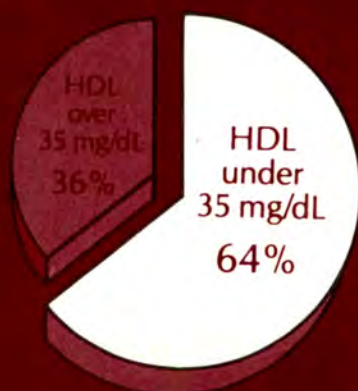
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CORONARY ARTERY DISEASE**291****Antiischemic and Metabolic Effects of Glutamate During Pacing in Patients with Stable Angina Pectoris Secondary to Either Coronary Artery Disease or Syndrome X**

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CORONARY ARTERY DISEASE

291**Antischemic and Metabolic Effects of Glutamate During Pacing in Patients with Stable Angina Pectoris Secondary to Either Coronary Artery Disease or Syndrome X**

Anne Thomassen, Torsten T. Nielsen, Jens P. Bagger, Anders K. Pedersen, and Per Henningsen

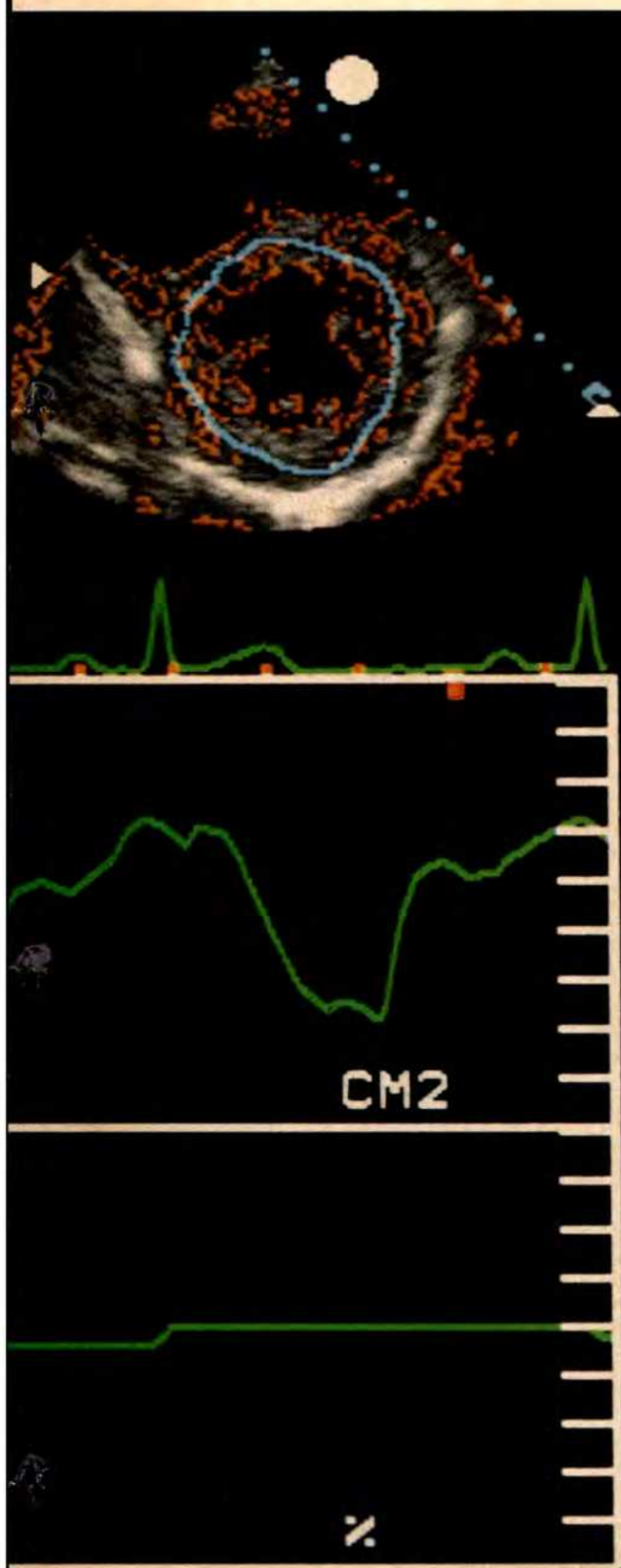
The effect of monosodium glutamate (1.2 or 2.5 mg/kg body weight administered intravenously) on anginal threshold, cardiac metabolism and hemodynamics were studied during 2 identical periods of coronary sinus pacing in 11 patients with stable angina pectoris, positive stress test results and pacing-induced cardiac lactate release due to coronary artery disease ($n = 9$) or syndrome X ($n = 2$). After glutamate, pacing time to onset of angina increased from 103 ± 53 to 166 ± 71 seconds ($p < 0.01$) and ST-segment depression decreased after pacing from 2.3 ± 1.0 to 1.6 ± 1.1 mm ($p < 0.01$). Arterial levels of glutamate increased 80% ($p < 0.001$) and myocardial glutamate uptake 25% ($p < 0.01$). Pacing-induced cardiac release of lactate ($n = 11$) diminished by 50% ($p < 0.05$). Arterial free fatty acids decreased 20% ($p < 0.01$). Circulating concentrations and cardiac exchanges of alanine, glucose, citrate, xanthine and hypoxanthine were unchanged. Glutamate did not influence heart rate, arterial blood pressure, coronary sinus blood flow or myocardial oxygen consumption. Glutamate was well tolerated. In conclusion, augmented provision of glutamate enhances pacing tolerance, presumably by a metabolic improvement of cardiac energy production during ischemia.

296**Angiographically Assessed Coronary Arterial Patency and Reocclusion in Patients with Acute Myocardial Infarction Treated with Anistreplase: Results of the Anistreplase Reocclusion Multicenter Study (ARMS)**

Lucy Relik-van Wely, Rombout F. Visser, Joop M. J. van der Pol, Ingrid Bartholomeus, Jaap E. Couvée, Henk Drost, André J. T. M. Vet, Huib C. Klomps, Wim A. A. J. van Ekel, Fred van den Berg, and X. Hanno Krauss

Coronary angiography was used to determine the patency of the infarct-related vessel in 156 patients with acute myocardial infarction 90 minutes and 24 hours after the administration of 30 U of anistreplase intravenously

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over 5 minutes. The results were compared with patency assessed by 3 noninvasive criteria (electrocardiographic changes, loss of chest pain, time to peak plasma creatine kinase). At 90 minutes, 73% of patients had a patent infarct-related vessel and at 24 hours 4% of patients had reocclusion of the infarct-related vessel. In cases in which at least 2 of the 3 noninvasive criteria indicated patency of the infarct-related vessel, there was a good correlation with the angiographically determined patency of the vessel.

301

Acute Effects of Intravenous Nicardipine on Hemodynamics and Cardiac Function in Patients with a Healed Myocardial Infarction and No Evidence of Congestive Heart Failure

Takeshi Ogawa, Tatsuhiko Sekiguchi, Masanori Ishii, Kazunori Ushiyama, Kazuhiko Yasui, and Yasuro Sugishita

Acute effects of intravenous nicardipine (10 μ g/kg) on systemic hemodynamics and cardiac function were evaluated in patients with a healed myocardial infarction and no evidence of congestive heart failure. Our data show that a small dose of nicardipine exerts a favorable effect on impaired diastolic function, but depresses left ventricular pump function with much less effect on right heart circulation.

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Comparative Efficacy and Safety of Bepridil and Diltiazem in Chronic Stable Angina Pectoris Refractory to Diltiazem

Bramah N. Singh, for the Bepridil Collaborative Study Group

This double-blind, multicenter study evaluated the efficacy and safety of bepridil (200 to 400 mg/day) in patients with chronic stable angina refractory to maximal tolerated doses of diltiazem (median 360 mg/day). After a 2-week baseline period with diltiazem, 86 patients were randomly assigned to either continue diltiazem (n = 40) or receive bepridil (n = 46). Antianginal efficacy was determined by angina frequency, nitroglycerin consumption and exercise treadmill testing. At the end of 8 weeks of double-blind therapy, changes in times to angina onset and 1 mm of ST-segment depression from baseline were significantly (p < 0.05) greater with bepridil than with diltiazem. The groups did not differ significantly in angina frequency or nitroglycerin consumption. Bepridil reduced heart rate by 4 beats/min (p < 0.001) and prolonged QTc by 35 ms (p < 0.001). The most frequent adverse effects were nausea, asthenia, dizziness, headache and diarrhea. The data indicate that bepridil provided safe and effective antianginal therapy in patients who exhibited less than optimal response to maximal tolerated doses of diltiazem.

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Safety and Efficacy of Percutaneous Transluminal Coronary Angioplasty in Patients with Left Ventricular Dysfunction

Tracy Stevens, Joel K. Kahn, Ben D. McCallister, Robert W. Ligon, Susan Spaude, Barry D. Rutherford, David R. McConahay, Warren L. Johnson, Lee V. Giorgi, Thomas M. Shimshak, and Geoffrey O. Hartzler

The results of 845 percutaneous transluminal coronary angioplasties in patients with left ventricular dysfunction (ejection fraction \leq 40%) were

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compared with 8,117 procedures in patients with ejection fractions $>40\%$. Patients with left ventricular dysfunction were older, had a greater incidence of 3-vessel disease and class IV angina than the control group. Angiographic success was lower (93 vs 95%, $p < 0.01$) and procedural mortality was increased (4 vs 1%, $p < 0.001$) in the study group. Survival at 1 and 4 years was 87 and 69%. These data suggest that percutaneous transluminal coronary angioplasty may be an effective treatment in patients with left ventricular dysfunction.

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Comparison of Exercise Radionuclide Angiography with Thallium SPECT Imaging for Detection of Significant Narrowing of the Left Circumflex Coronary Artery

Vasken Dilsizian, Pasquale Perrone-Filardi, Richard O. Cannon III, Nanette M. T. Freedman, Stephen L. Bacharach, and Robert O. Bonow

To determine whether regional dysfunction of the posterolateral wall on exercise radionuclide angiography is more sensitive in detecting left circumflex disease than thallium perfusion abnormalities assessed by single-photon emission tomography, 110 patients with significant coronary artery disease were studied, of whom 70 had a significant stenosis of the left circumflex coronary artery or a major obtuse marginal branch. Both regional function and segmental thallium activity of the posterolateral wall were assessed using visual and quantitative analyses. Qualitative posterolateral wall motion analysis detected 76% of patients with left circumflex coronary artery stenosis, with a specificity of 83% compared with only 44% by qualitative thallium tomography ($p < 0.001$) and a specificity of 92%. Whereas quantitation of thallium activity increased the sensitivity for detecting left circumflex coronary artery stenosis to 80% with a specificity of 55%, it did not achieve statistical significance when compared with qualitative wall motion analysis. Similarly, quantitation of the posterolateral regional function did not improve the sensitivity for detecting left circumflex coronary artery stenosis (74%) when compared with qualitative regional function. Thus, for noninvasive detection of left circumflex coronary artery disease, the data suggest that qualitative exercise radionuclide angiography is preferable to qualitative thallium single-photon emission computed tomography and provides comparable information to quantitative thallium analysis.

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Stunned Left Ventricular Myocardium After Exercise Treadmill Testing in Coronary Artery Disease

Robert A. Kloner, John Allen, Timothy A. Cox, Yuechun Zheng, and Carlos E. Ruiz

The purpose of this study was to investigate whether patients with known coronary artery disease developed prolonged wall motion abnormalities after exercise stress testing. We identified a group of patients with angiographically documented coronary artery disease who developed a worsening of echocardiographically evaluated wall motion from rest to 15 or 30 minutes, or both, after exercise. Wall motion score (1 = normal, 4+ = dyskinesia) in the midseptum increased from 1.0 at rest to 1.6 ($p < 0.004$) 30 minutes after exercise; basal inferior score worsened from 1.0 at rest to 1.9 ($p < 0.01$) 30 minutes after exercise. A group of normal adult volun-

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teers with no history of coronary artery disease did not reveal any wall motion abnormalities. In patients with coronary artery disease, exercise testing induced regional wall motion abnormalities of the left ventricle which were present for at least 30 minutes after exercise, consistent with the phenomenon of stunned myocardium.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

335**Serial Antiarrhythmic Drug Treatment to Maintain Sinus Rhythm After Electrical Cardioversion for Chronic Atrial Fibrillation or Atrial Flutter**

Harry J. Crijns, Isabelle C. Van Gelder, Wiek H. Van Gilst, Hans Hillege, A. Marcel Gosselink, and Kong I. Lie

To investigate whether serial drug treatment, using different types of antiarrhythmic drugs, favorably influences the postcardioversion arrhythmia prognosis, 127 patients with chronic atrial fibrillation or flutter were studied. Drugs used were flecainide (stage I), sotalol or quinidine (stage II) and finally amiodarone (stage III). On an actuarial basis the percentage of arrhythmia-free patients at the end of 2 years increased from 31% after stage I to 64% at the end of stage III. Factors predicting an unfavorable arrhythmia outcome despite serial treatment were older age, long previous arrhythmia duration, mitral valve disease, and a large number of previous episodes of chronic arrhythmia.

343**Different Mechanisms of Polyuria and Natriuresis Associated with Paroxysmal Supraventricular Tachycardia**

Takashi Fujii, Shunichi Kojima, Masahito Imanishi, Tohru Ohe, and Teruo Omae

The mechanism of polyuria associated with paroxysmal supraventricular tachycardia (SVT) was investigated in 8 patients. SVT was induced artificially and sustained for 60 minutes. Urine volume increased in the latter half of SVT and in 30 minutes after SVT. Urinary excretion of sodium increased after SVT ended. The level of plasma atrial natriuretic polypeptide (ANP) increased during SVT. Urinary excretion of antidiuretic hormone (ADH) decreased during SVT but increased after SVT. Urinary excretion of prostaglandin E_2 excretion increased after SVT. The percent changes in urinary prostaglandin E_2 were correlated with those in urinary ADH. A positive correlation was observed between the percent changes in the urinary excretion of prostaglandin E_2 and those in sodium. Polyuria during SVT was attributed mainly to inhibition of ADH secretion. Natriuresis after SVT was caused not only by increase of ANP but also by increase of renal prostaglandin E_2 associated with increased ADH secretion.

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Effect of Reflex Vagal Activation on Frequency of Ventricular Premature Complexes

Mario Facchini, Gaetano M. De Ferrari, Oscar Bonazzi, Theodore Weiss, and Peter J. Schwartz

The antiarrhythmic effect of vagal activation, reflex-induced by phenylephrine infusion, was evaluated in 17 patients with highly frequent ventricular premature complexes (VPCs). Baroreceptor activation could be obtained in 10 patients (responders), whereas it was inadequate in 7 (nonresponders). In the former group, when heart rate was allowed to fluctuate, the mean number of VPCs decreased from 38 ± 8 to $0.2 \pm 0.6/100$ beats ($p < 0.0001$). During atrial pacing at the preinfusion rate, VPCs reappeared but their mean number ($22 \pm 10/100$ beats) was still significantly reduced compared with control values ($p = 0.003$). In the nonresponders, VPC frequency was not affected. These results demonstrate that vagal activation markedly reduces VPCs. This effect is only partially rate-dependent; electrophysiologic changes secondary to baroreflexes are likely to be involved.

CONGESTIVE HEART FAILURE

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Left Ventricular Shape as a Determinant of Functional Mitral Regurgitation in Patients with Severe Heart Failure Secondary to Either Coronary Artery Disease or Idiopathic Dilated Cardiomyopathy

Tatsuji Kono, Hani N. Sabbah, Paul D. Stein, James F. Brymer, and Fareed Khaja

The relation between left ventricular (LV) shape and functional mitral regurgitation (MR) was evaluated in 39 patients with heart failure due to either coronary artery disease ($n = 23$) or dilated cardiomyopathy ($n = 16$). MR was present in 9 patients with coronary disease and in 10 with dilated cardiomyopathy. No difference was observed between patients with and without MR with regard to LV ejection fraction, LV chamber volume or regional wall motion abnormalities. However, regardless of the etiology of heart failure, patients with MR had a significantly more spherical left ventricle than patients without MR. These results indicate that in patients with heart failure, functional MR is present in those who manifest a more spherical left ventricle.

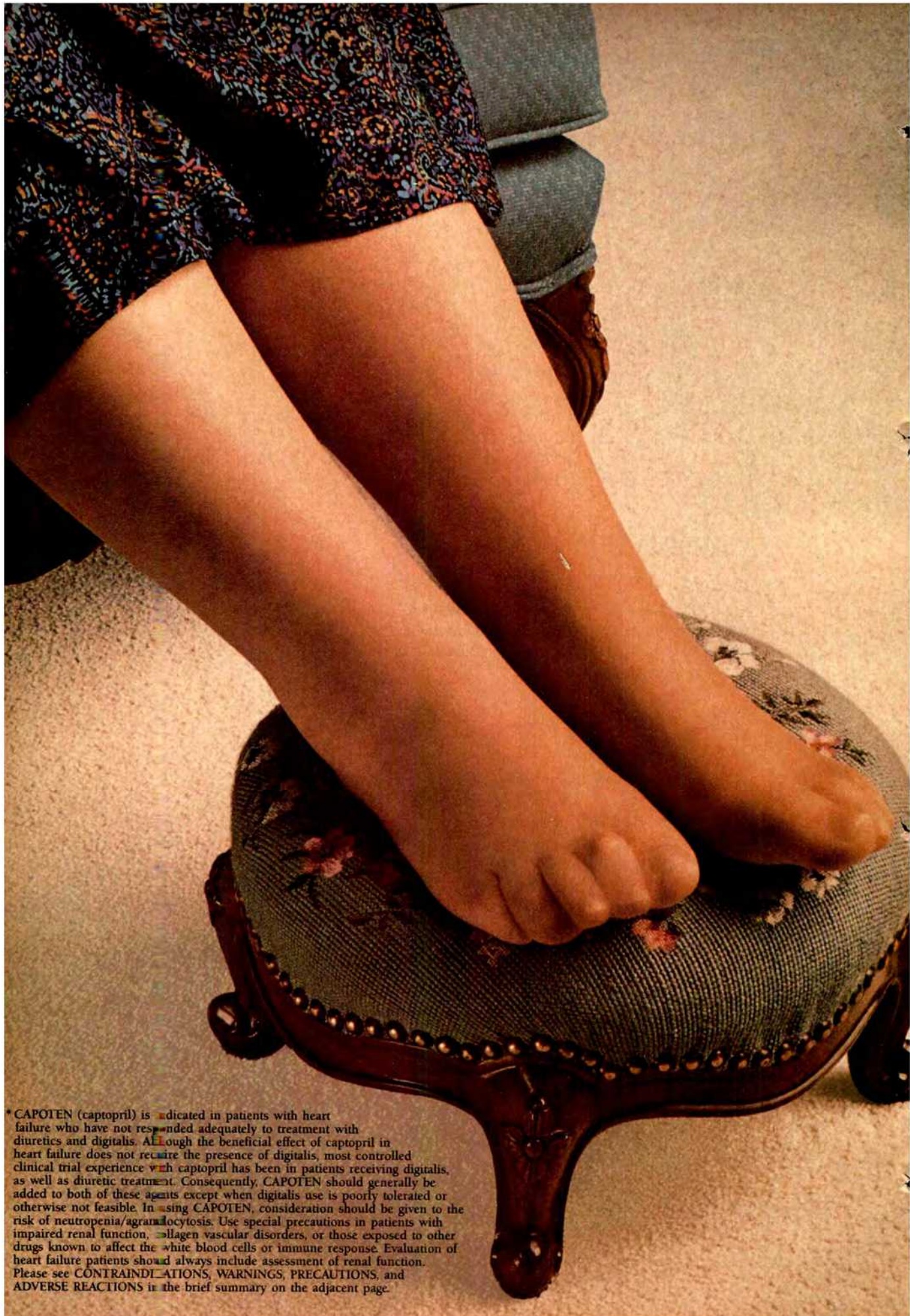
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Effects of Enoximone on Exercise Tolerance in Patients with Mild to Moderate Heart Failure

Haruki Itoh, Koichi Taniguchi, Mayumi Doi, Akira Koike, and Akira Sakuma

The efficacy of enoximone on exercise tolerance in patients with mild to moderate heart failure was evaluated in 33 patients. Cycle ergometer exercise testings using ramp protocol were performed before and 3 hours after administration of placebo, and 25 or 100 mg of enoximone which

Continued on page A39



* CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to treatment with diuretics and digitalis. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment. Consequently, CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white blood cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

were randomly allocated in a double-blind manner. Minute ventilation, oxygen uptake and carbon dioxide output were measured every 10 seconds in order to determine anaerobic threshold (AT) and peak oxygen uptake. Heart rate increased and systolic blood pressure decreased throughout exercise only in the 100-mg group ($n = 10$). AT and peak oxygen uptake increased significantly in the 100-mg enoximone group. The increasing ratio of ATs showed dose response, and the work rates at the AT point increased in both the 25- and 100-mg groups. These results indicate that a single oral administration of enoximone improves exercise tolerance in patients with mild to moderate heart failure.

CARDIOMYOPATHY**365****Outcome of Infants and Children with Dilated Cardiomyopathy**

Alan B. Lewis and Michelle Chabot

A review of 81 infants and children with dilated cardiomyopathy was undertaken to identify risk factors for poor outcome. Arrhythmias were present in only 8 of 51 survivors (16%) but were detected in 16 of 30 patients (53%) who died ($p < 0.05$). Patients dying suddenly were even more likely to have had documented dysrhythmias (8 of 11, 73%). Left ventricular end-diastolic pressure averaged 20.8 ± 1.6 mm Hg. Patients who died had a significantly higher left ventricular end-diastolic pressure than those who survived (29.5 ± 2.2 vs 15.0 ± 1.6 mm Hg, $p < 0.001$). Actuarial survival analysis revealed that mortality was highest during the first 6 months after presentation (19% mortality). Survival declined more gradually thereafter. Age at presentation did not have any significant impact on survival, although left ventricular end-diastolic pressure > 25 torr was associated with a significantly increased mortality rate ($p < 0.05$). Early cardiac transplantation should be considered in patients with markedly elevated left ventricular end-diastolic pressure or complex dysrhythmias, or both.

370**Effects of Immunosuppressive Therapy in Biopsy-Proved Myocarditis and Borderline Myocarditis on Left Ventricular Function**

Steven R. Jones, Ahvie Herskowitz, Grover M. Hutchins, and Kenneth L. Baughman

We studied the response to a 6- to 8-week course of prednisone and azathioprine in 20 patients with endomyocardial biopsy-proved myocarditis or borderline myocarditis by Dallas criteria. Endomyocardial biopsy and assessment of left ventricular (LV) function by echocardiography and right-sided cardiac catheterization was performed before and after completion of treatment. Significant improvement in heart rate-corrected mean velocity of circumferential shortening, LV ejection fraction and stroke work-end-diastolic volume ratio were found in the group with borderline myocarditis. LV end-diastolic and end-systolic volumes decreased significantly in the borderline group. No significant changes in indexes of LV function or LV volume occurred in the myocarditis group. Thus, short-term immunosuppressive therapy is associated with improve-

ment of LV function and regression of ventricular dilatation in patients with borderline myocarditis to a greater extent than in patients with myocarditis. Patients with borderline myocarditis should be considered for inclusion in subsequent trials of immunosuppressive therapy in myocarditis.

MISCELLANEOUS**377****Left Ventricular Filling Abnormalities in Asymptomatic Morbid Obesity**

Stuart W. Zarich, Glen J. Kowalchuk, Maureen P. McGuire, Peter N. Benotti, Edward A. Mascioli, and Richard W. Nesto

Indexes of left ventricular (LV) diastolic filling were measured by pulse Doppler echocardiography in 16 asymptomatic morbidly obese patients presenting for bariatric surgery and compared with an age- and sex-matched lean control population. Fifty percent of morbidly obese patients had LV diastolic filling abnormalities. The ratio of peak early to peak late (atrial) filling velocity was significantly decreased in obese compared with control subjects (1.16 ± 0.26 vs 1.66 ± 0.30 , $p < 0.001$). The peak velocity of early LV diastolic filling was significantly reduced in obese patients (75 ± 15 vs 98 ± 19 cm/s, $p < 0.001$). The atrial contribution to stroke velocity was significantly increased in obese patients (36 ± 7 vs $27 \pm 4\%$, $p < 0.001$). Obese patients had significantly increased LV mass indexes; however, increased LV mass did not correlate with indexes of abnormal LV diastolic filling in obese patients. These data suggest that abnormalities of diastolic function are common in the asymptomatic morbidly obese.

EDITORIALS**382****Principles and Practice of Coronary Thrombolysis and Conjunctive Treatment**

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389**Immunosuppressive Therapy and Lipoprotein Abnormalities After Cardiac Transplantation**

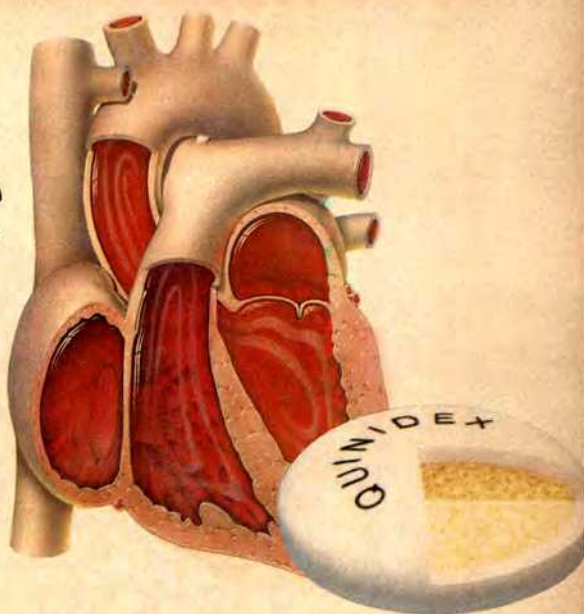
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BRIEF REPORTS**392****Myocardial Malondialdehyde and Uric Acid Release After Short-Lasting Coronary Occlusions During Coronary Angioplasty: Potential Mechanisms for Free Radical Generation**

I. K. De Scheerder, A. M. M. van de Kraay, J. M. J. Lamers, J. F. Koster, J. W. de Jong, and P. W. Serruys

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The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heart block. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained liver and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: General—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients:—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests:—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug
Quinidine with anticholinergic drugs
Quinidine with cholinergic drugs
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiamide diuretics
Quinidine with coumarin anticoagulants
Quinidine with tubocurarine, succinylcholine and decamethonium
Quinidine with phenothiazines and reserpine
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenyltin, rifampin)
Quinidine with digoxin
Quinidine with amiodarone
Quinidine with cimetidine
Quinidine with ranitidine
Quinidine with verapamil
Quinidine with nifedipine

Effect

Additive vagolytic effect
Antagonism of cholinergic effects
Alkalinization of urine resulting in decreased excretion of quinidine
Reduction of clotting factor concentrations
Potentiation of neuromuscular blockade
Additive cardiac depressive effects
Decreased plasma half-life of quinidine
Increased serum concentration of digoxin (See Warnings)
Increased serum concentration of quinidine
Prolonged quinidine half-life and an increase in serum quinidine level
Premature ventricular contractions and/or bigeminy
Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have zytotoxic properties. The significance of this property in the clinical setting has not been established.

Laboratory Tests:—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have zytotoxic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers:—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use:—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal:—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular:—Ventricular extrasystoles occurring at a rate of one or more every 5 normal beats, widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System:—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otic:—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic:—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity:—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic:—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic:—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous:—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

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Antiischemic and Metabolic Effects of Glutamate During Pacing in Patients with Stable Angina Pectoris Secondary to Either Coronary Artery Disease or Syndrome X

Anne Thomassen, MD, Torsten T. Nielsen, MD, Jens P. Bagger, MD,
Anders K. Pedersen, MD, and Per Henningsen, MD

The effects of glutamate on anginal threshold, cardiac metabolism and hemodynamics were studied in 11 patients with stable angina pectoris, positive stress test results, and pacing-induced myocardial lactate release due to coronary artery disease (CAD) ($n = 9$) or syndrome X ($n = 2$). Data were obtained before, during and after 2 identical periods of coronary sinus pacing, the second being preceded by an intravenous injection of monosodium glutamate 1.2 ($n = 7$) or 2.5 ($n = 4$) mg/kg body weight. After glutamate administration, pacing time to onset of angina increased from mean \pm standard deviation 103 ± 53 to 166 ± 71 seconds ($p < 0.01$) and ST-segment depression after pacing decreased from 2.3 ± 1.0 to 1.6 ± 1.1 mm ($p < 0.01$). Arterial glutamate concentration increased 60% ($p < 0.01$) after the low dose and 150% ($p < 0.01$) after the high dose of glutamate. Regardless of dose, myocardial glutamate uptake increased by 25% ($p < 0.01$). Pacing-induced cardiac release of lactate diminished 50% ($p < 0.05$), whereas the releases of xanthine and hypoxanthine were unchanged by glutamate. Arterial free fatty acids decreased 20% ($p < 0.01$). Circulating levels and cardiac exchanges of alanine, glucose and citrate were unchanged. Glutamate did not influence heart rate, arterial blood

pressure, coronary blood flow, coronary vascular resistance or myocardial oxygen consumption. One patient complained of short-lasting burning sensations after receiving the high glutamate dose.

In conclusion, augmented provision of glutamate enhances pacing tolerance in stable angina, presumably by a metabolic improvement of cardiac energy production during ischemia.

(Am J Cardiol 1991;68:291-295)

The human heart responds to ischemia by increasing its uptake of glutamate.¹⁻³ Global myocardial extraction of glutamate can be as much as 90% of the arterial contents in patients with coronary artery disease (CAD).² This suggests an almost complete extraction and perhaps an insufficient supply of glutamate to the ischemic areas,² leading to depletion of the intracellular glutamate stores.⁴⁻⁶ Augmented provision of glutamate preserves tissue glutamate contents⁴⁻⁶ and enhances mechanical function and recovery of ischemic heart in animal experiments^{4,5,7-10} and in humans with failing hearts.^{11,12} Furthermore, glutamate pretreatment may improve exercise tolerance in patients with stable angina pectoris.¹³

The exact mechanism of the cardioprotective effect of glutamate is uncertain. It has been associated with increased myocardial levels of high-energy phosphates.^{4-6,8,10} We recently demonstrated that even a very small dose of glutamate causes a change in myocardial substrate utilization, from preferentially free fatty acid toward preferentially glucose and glutamate consumption in patients without ischemic heart dis-

From the Department of Cardiology, Skejby Sygehus, DK 8200 Aarhus N, Denmark. This study was supported by grants from the Danish Heart Foundation and the Danish Medical Research Council. Manuscript received November 27, 1990; revised manuscript received and accepted March 25, 1991.

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ease.¹⁴ The metabolic effects of glutamate in the ischemic human heart are thus far unknown. The present study was undertaken to study the influence of intravenous glutamate on anginal threshold, cardiac substrate metabolism and coronary hemodynamics during pacing-induced ischemia in patients with stable angina due to either CAD or syndrome X.

METHODS

Patient group: The study included 11 patients, mean age \pm standard deviation 51 ± 9 years, with stable effort angina, positive exercise test results (>1 -mm ST depression) and pacing-induced myocardial release of lactate. The coronary angiograms were normal in 2 patients (syndrome X) and showed $>50\%$ fixed diameter reduction of at least 1 coronary artery in 9 patients (CAD). Seven patients had a history of myocardial infarction >6 months before the study. None of the subjects had signs of vasospastic angina or additional heart disease, systemic hypertension or metabolic disorders. None were treated with digitalis.

Procedures: After written informed consent, antianginal medication except for sublingual nitroglycerin was discontinued 1 week before the study. After the patients' overnight fast a Teflon® catheter was inserted into the distal aorta through a femoral artery for arterial blood sampling and pressure measurement. A Wilton-Webster thermodilution pacing catheter was advanced through an antecubital vein to midposition of the coronary sinus for blood sampling, pacing and flow measurement.¹⁵ The catheters were kept patent by intermittent flushing with saline solution to which 1,000 U of heparin had been added.

After 15 minutes of rest, coronary sinus pacing at a constant individual rate of 135 to 150 beats/min was performed until intolerable chest pain occurred, or to a maximal time of 10 minutes. To prevent atrioventricular block, 0.25 mg of atropine was given intravenously just before the start of pacing. Forty minutes after cessation of pacing, monosodium glutamate (25 mg/ml [148 mmol/liter]) was given as an intravenous bolus dose of 1.2 and 2.5 mg/kg body weight to 7 and 4 patients, respectively. Five minutes after glutamate injection, pacing was repeated at the same rate and duration as during the first period in each patient.

Electrocardiographic lead V_5 was continuously monitored. During both periods, duration of pacing to onset of chest pain was registered and the postpacing ST-segment depression (mean value 0.08 second in the first 4 sinus beats) was measured. Simultaneous arterial and coronary sinus blood samples were obtained, and coronary sinus blood flow, heart rate and blood pressure were determined 3 times at rest, twice during the last 2 minutes of pacing, and at 1, 3, 5 and 7 minutes of recovery. The blood samples were prepared and analyzed for contents in whole blood of oxygen, hemoglobin, hematocrit and lactate, and in plasma of glutamate, free fatty acids, glucose, citrate and alanine as previously described.¹⁴ For analysis of plasma xanthine and hypoxanthine¹⁶ blood samples obtained at rest and just before and after pacing were pooled.

Calculations and statistics: Values at rest are the means of 3 determinations. The rate-pressure product was determined as the systolic arterial blood pressure multiplied by heart rate. Coronary vascular resistance was calculated from mean arterial pressure divided by coronary sinus blood flow. Net substrate flux across the heart was calculated as arteriocoronary sinus concentration difference multiplied with coronary sinus blood flow for whole blood determinations and with 1 hematocrit for plasma measurements. Data are given as mean \pm standard deviation unless otherwise stated. Wilcoxon signed-rank test, and paired and unpaired t tests were applied for statistical evaluation. A probability value <0.05 was considered significant.

RESULTS

Only 1 patient complained of adverse effects from glutamate: facial pressure and burning sensations lasting for 30 to 60 seconds after the injection of 2.5 mg/kg. The effects of glutamate, apart from arterial glutamate levels, were not dose-related and did not differ between patients with CAD and those with syndrome X. Therefore, data from all patients are combined unless otherwise stated.

Pacing tolerance: All subjects developed typical chest pains and ST-segment depression during pacing, which was discontinued after 260 ± 108 seconds. After

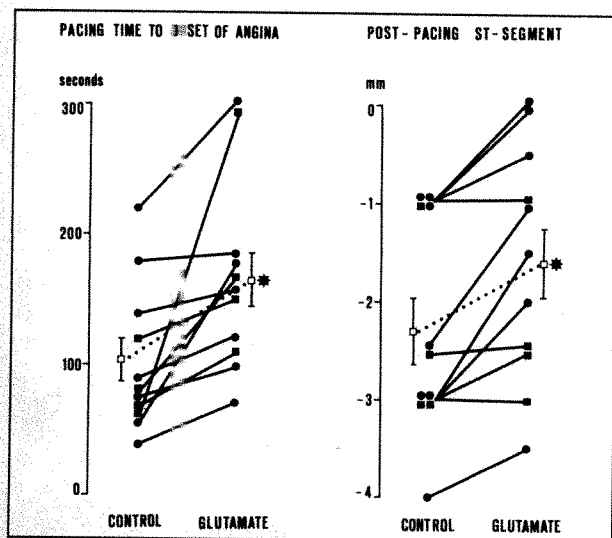


FIGURE 1. Time to onset of angina pectoris during and after pacing; ST-segment depression at control and after administration of monosodium glutamate (1.2 mg/kg [closed circles] or 2.5 mg/kg [squares]). Mean \pm standard error of the mean (open squares). Difference from control: * $p < 0.01$. POST = after.

glutamate administration, pacing time to onset of angina increased from 103 ± 53 to 166 ± 71 seconds ($p < 0.01$) and ST-segment depression after pacing diminished from 2.3 ± 1.0 to 1.6 ± 1.1 mm ($p < 0.01$) (Figure 1).

Hemodynamics and cardiac oxygen consumption (Table I): Glutamate did not consistently influence heart rate, arterial blood pressure, coronary sinus blood

flow, coronary vascular resistance or myocardial oxygen consumption. Heart rate was elevated after the first pacing period and persisted into the period after glutamate administration, presumably due to atropine administration.

Metabolic results (Table II): GLUTAMATE: Arterial glutamate concentration increased by an average of 80% ($p < 0.001$) after glutamate administration. The

TABLE I Hemodynamics and Myocardial Oxygen Uptake in Control State and After Glutamate

		Pacing			Recovery (minutes)			
		Rest	1.	2.	1	3	5	7
HR (beats/min)	Con	67 ± 9	$145 \pm 7^*$	$145 \pm 7^*$	$76 \pm 17^\dagger$	$77 \pm 16^\dagger$	$75 \pm 17^\dagger$	$74 \pm 15^\dagger$
	Glu	$74 \pm 12^\S$	$145 \pm 7^*$	$145 \pm 6^*$	73 ± 15	74 ± 13	73 ± 13	73 ± 11
MAP (mm Hg)	Con	97 ± 15	102 ± 15	102 ± 14	99 ± 15	99 ± 18	98 ± 18	97 ± 17
	Glu	98 ± 14	102 ± 12	102 ± 12	98 ± 14	96 ± 13	97 ± 14	98 ± 14
HR \times SAP \times 0.01	Con	92 ± 23	$183 \pm 25^*$	$184 \pm 24^*$	110 ± 39	109 ± 36	105 ± 36	101 ± 33
	Glu	101 ± 27	$182 \pm 24^*$	$183 \pm 23^*$	108 ± 25	101 ± 27	101 ± 27	97 ± 25
CSBF (ml/min)	Con	81 ± 25	$163 \pm 40^*$	$162 \pm 41^*$	$99 \pm 24^\dagger$	84 ± 22	83 ± 22	85 ± 22
	Glu	81 ± 23	$159 \pm 41^*$	$158 \pm 41^*$	$95 \pm 25^\dagger$	88 ± 21	87 ± 22	88 ± 22
CVR (mm Hg/min/ml)	Con	1.3 ± 0.4	$0.7 \pm 0.2^*$	$0.7 \pm 0.2^*$	1.1 ± 0.4	$0.9 \pm 0.2^\dagger$	$0.9 \pm 0.2^\dagger$	$0.9 \pm 0.3^\dagger$
	Glu	1.3 ± 0.5	$0.7 \pm 0.2^*$	$0.7 \pm 0.2^*$	1.1 ± 0.4	$0.9 \pm 0.2^\dagger$	$0.9 \pm 0.2^\dagger$	$0.9 \pm 0.3^\dagger$
Oxygen A-CS (ml/100 ml)	Con	12.5 ± 1.3	$11.5 \pm 1.3^\dagger$	$11.6 \pm 1.3^*$	$11.0 \pm 1.3^*$	$11.3 \pm 1.3^*$	$11.8 \pm 1.4^*$	$12.0 \pm 1.4^\dagger$
	Glu	12.2 ± 1.4	$11.5 \pm 1.5^\dagger$	$11.4 \pm 1.4^\dagger$	$10.9 \pm 1.3^*$	$11.2 \pm 1.2^\dagger$	$11.6 \pm 1.1^\dagger$	$11.6 \pm 1.3^\dagger$
Oxygen net flux (ml/min)	Con	10.0 ± 2.7	$18.7 \pm 4.7^\dagger$	$19.0 \pm 5.3^*$	10.8 ± 2.6	9.4 ± 2.6	9.7 ± 2.5	10.1 ± 2.5
	Glu	9.8 ± 2.6	$18.3 \pm 5.1^*$	$18.2 \pm 4.6^\S$	10.3 ± 2.9	9.8 ± 2.5	10.1 ± 2.8	9.8 ± 2.4

Data are mean \pm standard deviation. Values at rest are means of 3 determinations. Pacing values were obtained 1 minute (1.) and immediately (2.) before discontinuing pacing. Difference from respective values at rest: * $p < 0.001$; $^\dagger p < 0.05$; $^\S p < 0.01$. Difference from respective values in control state: $^\S p < 0.05$. A-CS = arteriocoronary sinus concentration difference; Con = control state; CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; Glu = glutamate; HR = heart rate; MAP = mean arterial pressure; SAP = systolic arterial pressure.

TABLE II Metabolic Results in Control State and After Glutamate

		Pacing			Recovery (minutes)			
		Rest	1.	2.	1	3	5	7
Glutamate								
A ($\mu\text{mol/liter}$)	Con	83 ± 34	80 ± 33	79 ± 34	80 ± 32	$76 \pm 33^\dagger$	$76 \pm 31^\dagger$	$78 \pm 34^{**}$
	Glu	$153 \pm 76^*$	$100 \pm 43^\dagger$	$99 \pm 41^\dagger$	$97 \pm 40^\dagger$	$91 \pm 38^\dagger$	$91 \pm 37^\dagger$	$92 \pm 37^\dagger$
A-CS ($\mu\text{mol/liter}$)	Con	39 ± 13	$21 \pm 8^\dagger$	$20 \pm 8^\dagger$	$26 \pm 12^\dagger$	$32 \pm 10^\dagger$	$33 \pm 12^\dagger$	$35 \pm 14^{**}$
	Glu	$49 \pm 19^\S$	$26 \pm 11^\dagger$	$26 \pm 10^\dagger$	$30 \pm 13^\dagger$	$37 \pm 13^{**}$	$38 \pm 12^{**}$	$41 \pm 14^\S$
Net flux ($\mu\text{mol/min}$)	Con	1.87 ± 0.98	2.16 ± 1.08	2.02 ± 1.02	1.53 ± 0.84	$1.60 \pm 0.74^\dagger$	$1.54 \pm 0.68^{**}$	1.70 ± 0.76
	Glu	$2.28 \pm 1.07^\S$	$2.40 \pm 1.26^\S$	$2.47 \pm 1.29^\S$	$1.61 \pm 0.86^\dagger$	$1.88 \pm 0.91^\dagger$	$1.93 \pm 0.87^\dagger$	$1.90 \pm 0.87^{**}$
Lactate								
A (mmol/liter)	Con	0.64 ± 0.24	0.64 ± 0.25	0.63 ± 0.25	0.66 ± 0.29	0.66 ± 0.27	0.64 ± 0.26	0.63 ± 0.24
	Glu	0.60 ± 0.26	0.61 ± 0.23	0.63 ± 0.22	$0.66 \pm 0.24^\dagger$	$0.63 \pm 0.22^{**}$	$0.60 \pm 0.22^\dagger$	$0.59 \pm 0.21^\S$
A-CS (mmol/liter)	Con	0.17 ± 0.14	$-0.01 \pm 0.20^{**}$	$-0.07 \pm 0.21^\dagger$	$-0.18 \pm 0.30^\dagger$	0.09 ± 0.21	0.15 ± 0.14	0.16 ± 0.14
	Glu	0.14 ± 0.13	0.02 ± 0.21	$-0.01 \pm 0.21^\dagger$	$-0.11 \pm 0.35^{**}$	0.10 ± 0.19	0.14 ± 0.13	0.15 ± 0.12
Net flux ($\mu\text{mol/min}$)	Con	7.7 ± 6.6	-1.1 ± 18.2	$-6.2 \pm 19.0^{**}$	$-11.3 \pm 21.9^{**}$	4.4 ± 10.9	7.0 ± 6.7	7.8 ± 6.1
	Glu	6.1 ± 5.5	0.9 ± 19.3	$-1.3 \pm 18.7^\dagger$	$-7.5 \pm 25.2^\dagger$	4.7 ± 9.8	6.3 ± 5.2	7.1 ± 5.2
Free Fatty Acids								
A (mmol/liter)	Con	0.63 ± 0.22	0.68 ± 0.28	0.70 ± 0.32	0.70 ± 0.26	$0.71 \pm 0.27^{**}$	$0.78 \pm 0.32^{**}$	$0.77 \pm 0.29^\dagger$
	Glu	0.58 ± 0.21	$0.59 \pm 0.22^\dagger$	$0.59 \pm 0.23^\dagger$	$0.59 \pm 0.23^\dagger$	$0.59 \pm 0.21^\S$	$0.59 \pm 0.22^\S$	$0.59 \pm 0.22^\S$
A-CS (mmol/liter)	Con	0.17 ± 0.05	0.17 ± 0.06	0.17 ± 0.06	0.18 ± 0.06	0.17 ± 0.05	0.17 ± 0.05	0.17 ± 0.06
	Glu	0.17 ± 0.04	$0.15 \pm 0.05^\dagger$	0.15 ± 0.06	0.15 ± 0.06	0.16 ± 0.05	0.16 ± 0.05	0.16 ± 0.04
Net flux ($\mu\text{g/min}$)	Con	8.4 ± 4.3	$15.5 \pm 6.3^\dagger$	$15.5 \pm 6.9^\dagger$	10.2 ± 4.1	8.0 ± 4.4	8.4 ± 3.6	8.8 ± 3.8
	Glu	8.2 ± 3.4	$13.6 \pm 4.9^\dagger$	$13.3 \pm 4.7^\dagger$	8.6 ± 4.0	8.0 ± 3.5	8.2 ± 2.6	8.4 ± 2.8

Data are mean \pm standard deviation. Values at rest are means of 3 determinations. Pacing values were obtained 1 minute (1.) and immediately (2.) before discontinuing pacing. Difference from respective values at rest: ** $p < 0.05$; $^\dagger p < 0.001$; $^\S p < 0.01$. Difference from respective values in control state: * $p < 0.001$; $^\S p < 0.01$; $^\dagger p < 0.05$. A = arterial concentration; other abbreviations as in Table I.

increases at rest were higher after administration of 2.5 mg/kg glutamate (from 91 ± 48 to 225 ± 71 $\mu\text{mol/liter}$, $p < 0.01$) than after administration of 1.2 mg/kg (from 74 ± 18 to 117 ± 47 $\mu\text{mol/liter}$, $p < 0.01$). Despite a rapid decline, arterial glutamate remained higher than control levels throughout the study. The augmented supply was associated with a 25% increase of myocardial glutamate consumption, but when comparing high- with low-dose glutamate, the net uptake did not differ (rest 2.44 ± 1.25 vs 2.20 ± 0.95 $\mu\text{mol/min}$, $p = \text{not significant [NS]}$).

LACTATE: Glutamate administration did not consistently alter arterial lactate levels or myocardial uptake of lactate at rest but it diminished the amount of lactate released from the heart during and immediately after pacing by 50% ($p < 0.05$) (Table II).

FREE FATTY ACIDS: Arterial free fatty acid concentrations increased during the control period (Table II) presumably due to heparin flushing of the catheters. Glutamate administration depressed arterial free fatty acids by 20% ($p < 0.01$) and tended to reduce myocardial fatty acid utilization, though only reaching significance during pacing.

XANTHINE AND HYPOXANTHINE: Baseline arterial levels of xanthine (683 ± 195 nmol/liter) and hypoxanthine ($1,423 \pm 636$ nmol/liter) remained stable throughout the study. The first pacing period induced significant cardiac release of both xanthine ($p < 0.05$) and hypoxanthine ($p < 0.01$) when compared with the values of arteriocardiac gradients at rest (xanthine, 6 ± 192 nmol/liter; hypoxanthine, 160 ± 547 nmol/liter) and of net flux (xanthine, 1 ± 7 nmol/min; hypoxanthine, 10 ± 30 nmol/min). Without reaching significance, glutamate tended to decrease the pacing-induced release of xanthine (arteriocardiac difference, -209 ± 188 vs -137 ± 152 nmol/liter [$p = \text{NS}$]; net flux, -18 ± 21 vs -12 ± 17 nmol/min [$p = \text{NS}$]) and hypoxanthine (arteriocardiac difference, $-1,147 \pm 1,163$ vs $-950 \pm 1,869$ nmol/liter [$p = \text{NS}$]; net flux, -80 ± 88 vs -66 ± 142 nmol/min [$p = \text{NS}$]).

GLUCOSE, CITRATE AND ALANINE: Glutamate administration did not significantly alter circulating levels or myocardial exchanges of glucose, citrate or alanine in this study (data not given).

DISCUSSION

In the present study, antiischemic properties of glutamate were manifest during pacing as delayed onset of angina, diminished ST-segment depression and reduced myocardial lactate production. Glutamate was well tolerated and its beneficial effects were accompanied by increased arterial levels and myocardial uptake of glutamate and decreased arterial free fatty acids. We have previously demonstrated good reproducibility of anginal

threshold as well as the metabolic and hemodynamic response to pacing when applying the present model to patients with CAD.¹⁷

Adverse effects of monosodium glutamate, the so-called Chinese Restaurant Syndrome includes burning sensations, facial pressure and chest pain.¹⁸ Adverse effects do not occur after glutamate, 1.2 mg/kg body weight, was given to almost all patients in the present study.^{13,14} The dose was chosen on the basis of a recent work showing that stimulation of myocardial glutamate uptake was not further enhanced by increasing this dose to 2.5 or even 5.0 mg/kg during nonischemic conditions.¹⁴ The present study revealed that doubling the dose to 2.5 mg/kg in 4 of the patients with ischemic heart disease did not augment the 25% elevation of myocardial glutamate consumption obtained after the low dose despite arterial levels twice as high. These results are at variance with those of Pisarenko et al¹² who reported a fivefold increase in arteriocardiac sinus plasma glutamate differences during glutamate infusion. However, this was obtained during 15-fold elevations of arterial glutamate in patients with cardiac failure after open heart surgery. It is not unlikely that the function of cardiac membranes,¹⁹ including the glutamate transport systems, may be disturbed in that particular situation.

Glutamate administration neither increased myocardial oxygen supply (coronary blood flow) nor depressed oxygen demand (rate-pressure product), leaving myocardial oxygen consumption unchanged. This finding suggests that glutamate exerted its beneficial effects by improving myocardial energy production despite unaltered oxygen restriction. In various experimental models^{4,5,8,10} and in humans,⁶ addition of glutamate to perfusates or cardioplegic solutions has been demonstrated to prevent or diminish the depletion of high-energy phosphates during ischemia or hypoxia. In the present study, the intracellular levels of adenosine triphosphatase (ATP) remain obscure, but the transcardiac release of the diffusible ATP catabolites xanthine and hypoxanthine²⁰ were not significantly modified by glutamate.

There are several metabolic pathways through which glutamate may promote ischemic myocardial energy balance. One effect is accomplished by its conversion to α -ketoglutarate and the subsequent replenishment of Krebs cycle intermediates that are depleted from the ischemic cell.^{5,7,21} By substrate phosphorylation of α -ketoglutarate to succinate, glutamate may contribute to anaerobic ATP formation.^{4,5,7} This amino acid fermentation appears to be of quantitative significance during hypoxia in dogs in vivo²² and in humans.²³ However, glucose and glycogen remain the most important energy sources in ischemia.^{24,25} The ini-

tial high rates of glycolysis are, however, rapidly inhibited owing to accumulation of lactate and reduced nicotinamide-adenine dinucleotide.^{24,26} In this study, myocardial lactate release was reduced after glutamate administration, confirming some earlier reports^{6,8,9} but contradicting others.^{4,5,7,10} Glutamate may diminish lactate accumulation by transamination with pyruvate, leading to the production of alanine instead of lactate.^{4,27} In contrast to other studies,^{4,5,11,12} our results failed to show an increase of myocardial alanine release after glutamate treatment. An alternative cause for the decreased lactate production after glutamate may be an increased breakdown of lactate and pyruvate due to improved removal and reoxidation of cytosolic-reduced nicotinamide-adenine dinucleotide.²⁶ This occurs through the malate-aspartate shuttle,²⁸ flux that is strictly dependent on a high intracellular glutamate concentration.²⁹ The intracellular glutamate pool is depleted during ischemia, but replenished by exogenous glutamate administration.⁴⁻⁶ Glutamate is also a potent stimulator of insulin secretion and a gluconeogenic substrate by which myocardial glucose consumption is increased.¹⁴ In the present results, increased insulin levels were evidenced from a decrease in free fatty acid levels.

The greatest limitations of this study are the open design and the rapid clearance of plasma glutamate, which impedes interpretation of the metabolic results. The antiischemic effects of glutamate need to be confirmed in a blinded study with low levels of glutamate administered continuously.

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Angiographically Assessed Coronary Arterial Patency and Reocclusion in Patients with Acute Myocardial Infarction Treated with Anistreplase: Results of the Anistreplase Reocclusion Multicenter Study (ARMS)

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In this open multicenter study, 156 patients with acute myocardial infarction received 30 U of anistreplase intravenously over 5 minutes within 4 hours of the onset of chest pain. The patency of the infarct-related vessel was determined by coronary angiography 90 minutes after anistreplase treatment, and also 24 hours after treatment, in patients with a patent infarct-related vessel at 90 minutes, to assess the reocclusion rate. The investigators categorized the infarct-related vessel as patent or occluded, and 2 independent cardiologists graded the infarct-related vessel according to the Thrombolysis in Myocardial Infarction (TIMI) perfusion criteria.

At the 90-minute assessment, 106 of 145 evaluable patients (73%) had patent infarct-related vessels, and 39 of 145 (27%) had occluded infarct-related vessels. Of the 139 independently assessed patients, 98 (71%) had TIMI grades 2 or 3 and 41 (29%) had TIMI grades 0 or 1. At the 24-hour assessment, 98 of 102 patients (96%) had a patent infarct-related vessel, and reocclusion had occurred in 4 of 102 patients (4%). Of the 94 independently assessed patients 90 (96%) had TIMI grades 2 or 3, and 4 (4%) had TIMI grades 0 or 1.

The reliability of noninvasive parameters as indicators of achieved patency of the infarct-related vessel was estimated by means of correla-

tion with patency assessed by coronary angiography. A significant correlation of 0.62 was found. The patency rate of 71 to 73% after use of anistreplase in patients with acute myocardial infarction corresponds with findings in earlier studies. The low reocclusion rate of 4% after use of anistreplase probably reflects the prolonged action of anistreplase.

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Thrombolytic therapy improves the clinical outcome of patients with an acute myocardial infarction (AMI).¹⁻⁴ Early reperfusion is important for preserving myocardial tissue and reducing morbidity and mortality.^{1,5,6} Studies have shown that early patency rates after thrombolytic therapy range from 50% after intravenous streptokinase to 75% after anistreplase, recombinant tissue-type plasminogen activator or pro-urokinase.^{4,7-13} Prevention of reocclusion appears to be important for the clinical outcome in patients with AMI,¹⁴ but this has been investigated in fewer studies. Available data show reocclusion rates from 3 to 15% with streptokinase, from 10 to 20% with recombinant tissue-type plasminogen activator and from 3 to 9% with anistreplase.^{7-13,15-19}

Anistreplase is a streptokinase and plasminogen complex, with an anisoyl group reversibly placed within the catalytic center of the plasminogen moiety, a modification that does not affect the fibrin-binding capacity of the molecule. In circulation, anistreplase is deacylated to its active form at a controlled rate. This, in addition to the protection afforded by acylation from neutralization by circulating antiproteases, results in a longer circulating half-life for anistreplase: approximately 90 minutes compared with approximately 15 to 20 minutes for streptokinase, 9 minutes for recombinant tissue-type plasminogen activator and 5 minutes for pro-urokinase. These characteristics prolong the

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thrombolytic activity of anistreplase and might contribute to a lower incidence of early reocclusion.²⁰

In a previous study in the Netherlands,¹⁶ patients treated with anistreplase had a low reocclusion rate 24 hours after treatment (1 of 22, 5%). We designed this study to obtain further information on reocclusion within 24 hours of anistreplase, in relation to patency 90 minutes after treatment, in a larger population of patients with AMI.

Coronary angiography is less likely to be a standard clinical practice in the future for a variety of reasons: the nonavailability of catheterization laboratories, the now proven efficacy of thrombolysis, budgetary considerations and an increased risk of bleeding. Therefore, we also looked to noninvasive clinical indicators of patency²¹⁻²⁷ — changes in electrocardiographic assessments, time to peak serum creatine kinase and decrease of chest pain after thrombolytic therapy — to determine whether there is a reliable correlation between patency assessed by noninvasive criteria and patency assessments by coronary angiography. If a reliable correlation can be shown, then noninvasive criteria could become increasingly important in assessing the efficacy of thrombolytic therapy.

METHODS

Patients: One hundred fifty-six patients (131 men and 25 women) ranging in age from 33 to 78 years (mean 57) were recruited into this multicenter study from 8 centers (4 to 45 patients per center).

To be admitted to the study, patients had to be aged ≤ 70 years and to have had chest pain suggestive of acute myocardial ischemia lasting ≥ 20 minutes and ≤ 4 hours' duration, which was not relieved by nitrates. In addition there had to be electrocardiographic evidence of transmural myocardial infarction, shown by ST-segment elevations ≥ 0.1 mV in at least 1 standard lead or ≥ 0.2 mV in at least 1 precordial lead, or both, which persisted ≥ 5 minutes after administration of nitrates. Patients had to have no contraindications to thrombolytic therapy and all gave informed consent.

Five of the 156 patients were considered ineligible for the efficacy analysis because they had not fulfilled the entry requirements; 2 patients were >70 years of age and 3 patients did not fulfill the electrocardiographic criteria. The safety analysis includes all 156 patients.

Treatment: Patients received a standard intravenous dose of 100 mg of methylprednisolone, followed by 30 U of anistreplase (Eminase™) administered intravenously over 5 minutes. Heparin infusion, at 1,000 U/hour, was started 3 hours after thrombolytic therapy and was continued until effective oral anticoagulation was achieved, or for ≥ 24 hours.

Angiographic evaluation: Coronary angiography was performed 90 ± 30 minutes after administration of

TABLE I Baseline Characteristics

	Treated	Eligible
Total no.	156	151
Men/women	131/25	126/25
Age (years)	57 (range 33–78)	56 (range 33–70)
Treatment delay mean (hours)	2.15	2.15
< 1	12%	12%
1–2	31%	32%
2–3	35%	35%
3–4	21%	20%
> 4	1%	1%
Site of infarction		
Anterior + lateral	69 (44%)	67 (44%)
Inferior	87 (56%)	84 (56%)

anistreplase. If the infarct-related vessel was patent, coronary angiography was repeated at 24 ± 6 hours. The coronary angiograms were interpreted by the investigators who scored the infarct-related vessel "patent" or "not patent." An independent assessment was made by 2 other cardiologists who scored the infarct-related vessel according to the TIMI⁷ grading for coronary artery perfusion.

Noninvasive patency assessments: Cardiac enzymes (creatinine kinase and creatine kinase-MB) were assessed on entry and at 6, 12, 18 and 24 hours after administration of anistreplase. Electrocardiographic assessments were made on entry to the study and 1 and 2 hours after therapy. The severity of chest pain and the occurrence of arrhythmias were recorded 1 and 2 hours after administration of anistreplase.

To assess the reliability of noninvasive parameters as indicators of patency, the investigators also recorded whether they considered patency had been achieved using the following criteria: a reduction in chest pain within 2 hours of thrombolytic therapy; an improvement in electrocardiographic reading, i.e., a reduction in ST-segment elevation to ≤ 0.1 mV in at least 1 standard lead or ≤ 0.2 mV in ≥ 1 precordial leads, or both, within 2 hours of thrombolytic therapy; and a peak in the increase in creatine kinase within 15 hours of thrombolytic therapy. These 3 criteria were given equal weighting as positive indications of patency. The number of patients with angiographically demonstrated patency of the infarct-related vessel (investigators' assessment) was compared with the number of positive noninvasive assessments per patient, which could vary from 0 to 3. If a noninvasive assessment could not be made, it was considered "negative" in the analysis.

Follow-up assessments: At discharge from the hospital and 2 months after hospital admission the following occurrences were recorded: reinfarction, mortality, angina pectoris and heart failure, and whether percutaneous transluminal coronary angioplasty or coronary artery bypass grafts had been performed.

TABLE II Relation Between Number of Noninvasive, Clinical Criteria and Angiographically Assessed Patency

Clinical Data	Coronary Angiographic Data		
No. of Positive Assessments	Patients with Patent IRV	Patients with Occluded IRV	% Patency
2 of 3	67	6	92
2 of 3	32	10	76
1 of 3	4	15	21
0 of 3	0	6	0
≥ 1 missing	3	2	
Total (n = 145)	106	39	73

IRV = infarct-related vessel.

IRV = infarct-related vessel.

Adverse events: The occurrence of adverse events was recorded during the stay in the hospital and again 2 months after treatment.

Statistical analysis: Main efficacy and safety data are analyzed by means of descriptive methods, expressed in frequencies and percentages.

Reliability of noninvasive parameters was estimated by the phi coefficient, a measure of association for 2 × 2 contingency tables.

RESULTS

The baseline characteristics of the patients enrolled are summarized in Table I.

Coronary angiography at ninety minutes: Coronary angiography was performed 90 minutes (range 40 to 180, mean 96) after administration of anistreplase in 145 of the 151 patients eligible for this assessment. The investigators considered 106 patients (73%) to have patent infarct-related vessels and 39 patients (27%) to have occluded infarct-related vessels.

Six patients did not undergo coronary angiography: 2 patients died of cardiogenic shock 25 and 40 minutes after therapy; no catheterization laboratory was available for 2 patients; in 1 patient coronary angiography could not be performed because of tortuous iliac vessels; and in 1 patient the reason was unknown.

An independent assessment was made of 139 of the 145 patients who underwent coronary angiography at 90 minutes. Of these, 29 (21%) and 69 (50%) patients were classified as having TIMI grades 2 or 3, respectively, and 26 (18%) and 15 (11%) patients were classified as having TIMI grades 0 or 1, respectively.

No independent assessment was made for 6 patients: In 2 patients the infarct-related vessel could not be identified and the film for 4 patients was missing.

Coronary angiography at twenty-four hours: Of the 106 patients who had a patent infarct-related vessel at 90 minutes, 102 underwent coronary angiography at 24 hours. Reocclusion was found in 4 patients (4%),

whereas the infarct-related vessel was still patent in 98 patients (96%).

Four patients did not have a second coronary angiogram: 1 patient had had a cerebrovascular accident and subsequently died, and 3 patients were transferred to another hospital for percutaneous transluminal coronary angioplasty or coronary artery bypass graft (in 2 patients no reocclusion had occurred by 24 hours and in the other patient reocclusion occurred within 24 hours, during the percutaneous transluminal coronary angioplasty).

The independent assessment of 24-hour coronary angiograms was performed in 94 patients. Of these, 18 (19%) and 72 (77%) patients were classified as having TIMI grades 2 or 3, respectively, and 4 (4%) and 0 (0%) patients were classified as having TIMI grades 0 or 1, respectively.

Change in thrombolysis in myocardial infarction trial gradings: Changes in TIMI grades between 90 minutes and 24 hours were examined. Nine of the 29 patients with TIMI grade 2 perfusion at 90 minutes had TIMI grade 3 perfusion at 24 hours. Furthermore, 27 of the 41 patients with TIMI grade 0 or 1 at 90 minutes had a second coronary angiogram recorded, although this was not required by the protocol: 15 of these patients had TIMI grade 2 or 3 at 24 hours.

Noninvasive assessments of patency: Seventy-three patients had 3 of 3 positive noninvasive assessments; of these, 67 (92%) had angiographic evidence of infarct-related vessel patency. Of 42 patients with 2 of 3 positive noninvasive assessments, 32 (76%) had angiographic evidence of infarct-related vessel patency. Only 4 of 19 (21%) and 0 of 6 (0%) patients with 1 or no positive noninvasive assessments, respectively, had angiographic evidence of patency (see Table II). When 2 of the 3 criteria indicate that the infarct-related vessel is patent, then there is a significant correlation between noninvasive patency assessments and patency determined by coronary angiography (phi coefficient = 0.62, chi-square = 51.29, $p < 0.0001$).

Follow-up assessments: Of the 156 patients with AMI, 15 had reinfarction during their stay in the hospital. At the 2-month follow-up, 3 more of the 146 patients assessed appeared to have had a reinfarction. Thus, the incidence of reinfarction within 2 months was 18 of 156 (11.5%). Mean time between treatment and reinfarction was 3.3 days.

Postinfarction angina pectoris occurred in 39 of the 156 patients during their stay in the hospital: at 2-month follow-up, only 25 patients had angina pectoris. Heart failure occurred in 25 of the 156 patients during admission, but had occurred in only 4 patients before the 2-month follow-up visit.

Forty of the 156 patients had undergone percutaneous transluminal coronary angioplasty before discharge from the hospital, and another patient before the 2-month follow-up visit. A coronary artery bypass graft was performed in 12 patients before discharge from the hospital and in 5 others before the 2-month follow-up. Mean time between therapy and percutaneous transluminal coronary angioplasty was 8 days, and between therapy and a coronary artery bypass graft, 22 days.

At discharge 111 patients (76%) were receiving oral anticoagulant therapy, 12 patients (8%) acetylsalicylic acid, 41 patients (28%) dipyridamole, 73 patients (50%) nitrates, 68 patients (46%) calcium entry blockers, and 50 patients (34%) β blockers.

Adverse events: Adverse events after anistreplase were generally those expected with a thrombolytic agent. Thirty-four patients had hemorrhage or hematoma, or both, but none required a blood transfusion. Seven patients had allergic reactions, including skin rash and fever. Nineteen patients had hypotension; in 7, it was considered to be related to anistreplase. The hypotension resolved in all patients with or without treatment. Two patients had hemorrhagic cerebrovascular accidents, both of which were considered to be related to anistreplase. One of these patients died (see later) and the other recovered with minor sequelae.

Nine patients died during their stay in the hospital and another died before the follow-up visit, giving a 2-month mortality of 6.4%. Mean time between treatment and death was 3.9 days. Seven patients died in cardiogenic shock between 20 minutes and 4 days after anistreplase administration; 1 patient died of a hemorrhagic cerebrovascular accident 31 hours after anistreplase administration; 1 patient died of heart failure 7 days after anistreplase administration; and 1 patient died of ventricular arrhythmias after a coronary artery bypass graft 22 days after therapy.

Other adverse events were typical of those expected after AMI, mostly arrhythmias not requiring treatment.

DISCUSSION

This open multicenter study, in which anistreplase was administered to patients with AMI within 4 hours of the onset of chest pain, is among the largest patency studies with anistreplase and one of the few angiographically assessed reocclusion studies with thrombolytic therapy.

The patency rate of 71 to 73% at 90 minutes is consistent with that found in previous studies with anistreplase¹¹⁻¹³ and is higher than the patency reported with intravenous streptokinase (50%),^{7,8,11} and comparable with the patency achieved with recombinant

tissue-type plasminogen activator and pro-urokinase (75%)⁷⁻¹⁰ in other studies. However, no control group was used in this study and there are procedural differences between this study and those with other thrombolytic agents.

The reocclusion rate of 4% at 24 hours is low and is consistent with findings in previous studies of anistreplase^{12,15,16} although with fewer patients. This low reocclusion rate may be attributable to the long duration of action of anistreplase.²⁰ The improvement seen in TIMI gradings between 90 minutes and 24 hours in some patients (from TIMI grade 2 to 3 in 9 of 29 patients and from TIMI grade 0 or 1 to 2 or 3 in 15 of 27 patients) could also be attributable to the long duration of action of anistreplase.

The use of other therapies after thrombolysis is also important in the prevention of reocclusions.²⁸ In this study, the use of acetylsalicylic acid was not standard (the protocol was designed before the results of the International Study of Infarct Survival-II study²⁸ were available) and only 8% of the patients were receiving acetylsalicylic acid at discharge from the hospital. This might explain the relatively high reinfarction rate of 11.5% within 2 months, compared with that seen after streptokinase followed by acetylsalicylic acid.

Several trials have investigated the relation between noninvasive assessments of reperfusion of the infarct-related vessels and the angiographically determined patency of these vessels. A rapid increase and early peak 15 to 18 hours after thrombolytic therapy in creatine kinase has been found to be strongly indicative of reperfusion^{22,23,24,26} as has an early decrease in ST-segment elevation^{25,27} and chest pain. In this study, we investigated whether consideration of these noninvasive criteria in combination would give a good correlation with the findings of angiographic assessments. It was found that when 2 of the 3 criteria indicate that the infarct-related vessel is patent, then there is a good correlation between noninvasive patency assessments and patency determined by coronary angiography (phi coefficient = 0.62, chi-square = 51.29, $p < 0.0001$). Thus, noninvasive criteria appear to be reliable indicators that patency has been achieved.

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Acute Effects of Intravenous Nicardipine on Hemodynamics and Cardiac Function in Patients with a Healed Myocardial Infarction and No Evidence of Congestive Heart Failure

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Acute effects of intravenous nicardipine (10 $\mu\text{g}/\text{kg}$) on systemic hemodynamics and cardiac function were evaluated in 17 patients with a healed myocardial infarction and no evidence of congestive heart failure. Mean New York Heart Association functional class was 1.6 ± 0.5 (mean \pm standard deviation). Aortic systolic pressure ($p < 0.001$) and left ventricular end-diastolic pressure decreased (10 ± 3 to 8 ± 3 mm Hg, $p < 0.01$), and systemic vascular resistance decreased significantly ($p < 0.001$), whereas pulmonary and right atrial pressure and pulmonary arteriolar resistance did not change. Cardiac and stroke indexes showed biphasic changes. Although positive and negative maximal rate of left ventricular pressures decreased significantly ($p < 0.05$ and $p < 0.01$, respectively), they did not change significantly when aortic systolic pressure was corrected. There was a significant inverse correlation between the negative rate of left ventricular pressure/aortic systolic pressure before nicardipine infusion and its maximal percent increase after infusion ($r = -0.56$, $p < 0.05$), indicating a beneficial effect on diastolic relaxation in patients with impaired diastolic function.

Our data show that a low dose (10 $\mu\text{g}/\text{kg}$) of intravenous nicardipine exerts a favorable effect on impaired diastolic function, but depresses left ventricular pump function with much less effect on right heart circulation.

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Although there are many reports describing the effects of intravenous nicardipine,¹⁻⁵ it has become increasingly clear that its in vitro and in vivo effects on cardiac function differ markedly.⁶⁻⁸ In addition, there are conflicting clinical data regarding the effects of nicardipine on systemic circulation and cardiac function. Possible explanations for the inconsistency of these results include differing patient populations, the dosages of nicardipine and basal hemodynamic status.⁹ Most earlier investigations of patients with a previous myocardial infarction were performed in patients with high left ventricular filling pressure.¹⁻⁴ To our knowledge, few reports are available focusing on patients with a previous myocardial infarction without evidence of congestive heart failure. Accordingly, this study characterizes effects of intravenous nicardipine on the systemic circulation and cardiac function of patients with a healed myocardial infarction and no evidence of congestive heart failure.

METHODS

Patients: The study group consisted of 17 patients with a previous myocardial infarction (mean age \pm standard deviation 55 ± 9 years, range 38 to 75). Previous myocardial infarction was diagnosed by a typical history of chest pain, electrocardiographic changes and increased serum cardiac enzymes. All patients were in New York Heart Association functional class I or II and had a left ventricular end-diastolic pressure ≤ 15 mm Hg. The average interval between the onset of symptoms and the current protocol was 3.4 ± 0.8 months. No cardiac medications were administered within 24 hours of the study. All patients gave voluntary informed consent.

Hemodynamic studies: At least 30 minutes after diagnostic catheterization and coronary arteriography,¹⁰ a 7Fr pigtail catheter was placed in the left ventricle from a femoral artery, and a 7Fr balloon-tipped thermodilution catheter was inserted from a femoral vein and advanced until its tip was positioned in the right pulmonary artery. Left ventricular end-diastolic pressure and positive and negative maximal rate of left ven-

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TABLE I Acute Effects of Intravenous Nicardipine on Systemic Circulation

	Before Nicardipine	After Nicardipine (minutes)			
		1	5	15	30
ASP (mm Hg)	107 ± 8	95 ± 7*	96 ± 8*	100 ± 8*	102 ± 8
ADP (mm Hg)	64 ± 7	58 ± 8*	61 ± 8†	61 ± 8	65 ± 8
LVEDP (mm Hg)	10 ± 3	9 ± 5	8 ± 3†	9 ± 4†	8 ± 3†
PSP (mm Hg)	18 ± 3	19 ± 4	18 ± 4	18 ± 4	17 ± 4
PDP (mm Hg)	9 ± 3	9 ± 2	9 ± 3	9 ± 3	9 ± 3
RAP (mm Hg)	5 ± 2	5 ± 2	6 ± 2	6 ± 2	5 ± 2
HR (beats/min)	69 ± 13	72 ± 14†	70 ± 13	68 ± 14	68 ± 14
RPP (×10 ⁻³)	73.2 ± 14.6	68.3 ± 14.2†	66.3 ± 13.7†	68.2 ± 13.7†	69.0 ± 14.3†
CI (liters/min/m ²)	3.3 ± 0.8	3.5 ± 0.8†	3.3 ± 0.7	3.0 ± 0.5†	2.9 ± 0.5†
SI (ml/beat/m ²)	48 ± 12	50 ± 15	48 ± 12	46 ± 11	44 ± 9†
SVR (dynes · s · cm ⁻⁵)	1,222 ± 297	989 ± 245*	1,089 ± 286†	1,186 ± 244	1,284 ± 250
PAR (dynes · s · cm ⁻⁵)	57 ± 18	61 ± 29	58 ± 24	58 ± 23	61 ± 27
LVS WI (g · min/m ²)	48 ± 11	43 ± 11†	43 ± 11†	42 ± 10*	42 ± 9*
RVS WI (g · min/m ²)	4.7 ± 2.3	5.0 ± 2.9	4.4 ± 2.6	4.0 ± 2.5†	4.0 ± 2.2

Values are mean ± standard deviation.
 *p < 0.001; †p < 0.05; ‡p < 0.01.
 ADP = aortic diastolic pressure; ASP = aortic systolic pressure; CI = cardiac index; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVS WI = left ventricular stroke work index; PAR = pulmonary arteriolar resistance; PDP = pulmonary diastolic pressure; PSP = pulmonary systolic pressure; RAP = right atrial pressure; RPP = rate-pressure product; RVS WI = right ventricular stroke work index; SI = stroke index; SVR = systemic vascular resistance.

tricular pressures (positive and negative dP/dtmax) were recorded with the pigtail catheter. Thereafter, the pigtail catheter was withdrawn until its tip was positioned in the ascending aorta, and aortic pressure was measured. Pulmonary artery and right atrial pressures were recorded with the thermodilution catheter. Mean aortic, pulmonary artery and right atrial pressures were determined by electrical damping. The electrocardiogram was recorded simultaneously on a multichannel photographic recorder at paper speeds of 50 or 100 mm/s. Heart rate and pressure data from 3 cardiac cycles were averaged. Cardiac output was determined in triplicate by thermodilution method, using a cardiac output computer (COM-1, American Edwards Laboratories) and results were averaged. Rate-pressure product, cardiac index, stroke index, systemic vascular and pulmonary arteriolar resistance, and left and right ventricular stroke work index were calculated using standard formulas. Furthermore, left ventricular

positive and negative dP/dtmax were adjusted for aortic systolic pressure (positive and negative dP/dtmax/aortic systolic pressure) to correct for the influence of afterload on left ventricle.

Study design: After control measurements of pressure and cardiac output had been obtained and hemodynamic stability was established, 10 µg/kg of nicardipine was infused via the proximal portion of the thermodilution catheter for 2 minutes. The reason for choosing that dose was because low doses of intravenous nicardipine have been reported to develop predominant effects on vascular smooth muscle and much less effects on myocardium in dogs.⁸ In addition, high doses (5 to 10 mg) of intravenous nicardipine, used by most investigators in previous clinical studies, have been reported to induce striking decreases in aortic systolic pressure (20 to 30 mm Hg).^{1,3,4,9} Measurements of pressure and cardiac output were repeated in the same manner 1, 5, 15 and 30 minutes after termination of the infusion, as previously described (Figure 1).

Statistical analyses: All data are presented as mean ± standard deviation. Student's *t* test and linear regression analysis were used for statistical evaluations. Differences were considered significant at p < 0.05.

RESULTS

Hemodynamics: There were 6 patients in New York Heart association functional class I and 11 in class II. Aortic systolic pressure decreased significantly 1, 5 and 15 minutes (all p < 0.001), and aortic diastolic pressure decreased 1 and 5 minutes (p < 0.001 and p < 0.05, respectively) after termination of nicardipine infusion (Table I). Left ventricular end-diastolic pressure decreased significantly at 5, 15 and 30 minutes (p < 0.05,

	Before	Nicardipine 10 µg/kg/2min	After			
			1	5	15	30(min)
Pressure	○		○	○	○	○
Cardiac output	○		○	○	○	○

FIGURE 1. Measurements of pressure and cardiac output (circles) were performed before, and 1, 5, 15 and 30 minutes after intravenous infusion of nicardipine (10 µg/kg) for 2 minutes.

TABLE II Acute Effects of Intravenous Nicardipine on Left Ventricular Systolic and Diastolic Function

	Before Nicardipine	After Nicardipine (minutes)			
		1	5	15	30
Positive dP/dtmax (mm Hg/s)	1,368 ± 269	1,258 ± 348	1,289 ± 299*	1,300 ± 298	1,312 ± 304
Negative dP/dtmax (mm Hg/s)	1,129 ± 187	1,027 ± 233†	1,025 ± 207*	1,116 ± 217	1,120 ± 158
Positive dP/dtmax	1.2 ± 0.3	1.3 ± 0.3	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.2
Negative dP/dtmax					
Positive dP/dtmax/ASP (/s)	12.7 ± 2.8	13.3 ± 3.7	13.5 ± 3.5	12.9 ± 3.0	12.6 ± 2.2
Negative dP/dtmax/ASP (/s)	10.5 ± 1.5	10.7 ± 2.0	10.5 ± 1.7	11.0 ± 1.5	10.9 ± 1.2

Values are mean ± standard deviation.

*p < 0.05; †p < 0.01.

ASP = aortic systolic pressure; dP/dtmax = maximal rate of left ventricular pressure.

p < 0.05 and p < 0.01, respectively). However, pulmonary systolic and diastolic pressures and mean right atrial pressure did not change. Heart rate increased 1 minute after the end of infusion (p < 0.05), but rate-pressure product decreased throughout the 30-minute postinfusion protocol (p < 0.05 to p < 0.01). Cardiac index responded biphasically. It increased 1 minute (p < 0.05) and decreased 15 and 30 minutes (p < 0.05 and p < 0.01, respectively) after infusion. However, stroke index only decreased after 30 minutes (p < 0.05). Systemic vascular resistance decreased significantly 1 and 5 minutes after completion of infusion (both p < 0.01), while pulmonary arteriolar resistance did not change. There was no significant correlation between the magnitude of decrease (percent) in systemic vascular and pulmonary arteriolar resistances (Figure 2).

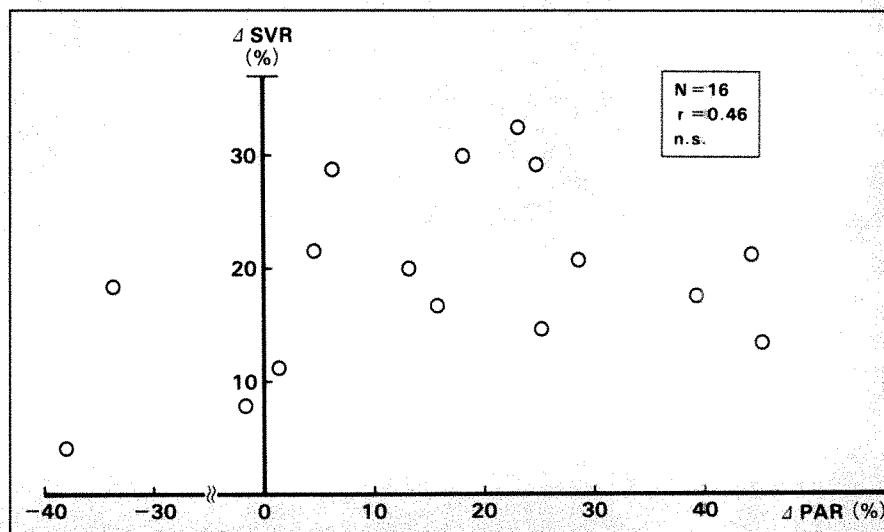
Ventricular function: Positive dP/dtmax decreased significantly 5 minutes after termination of infusion (p < 0.05) and negative dP/dtmax decreased after 1 and 5 minutes (p < 0.01 and p < 0.05, respectively) (Table II). However, positive and negative dP/dtmax adjusted for aortic systolic pressure remained constant (Table II). There was no significant correlation be-

tween positive dP/dtmax/aortic systolic pressure before and its maximal percent increase after infusion (Figure 3A). In contrast, a significant inverse correlation was found between negative dP/dtmax/aortic systolic pressure before infusion and its maximal percent increase afterward (r = -0.56, p < 0.05) (Figure 3B). Left ventricular stroke work index decreased significantly throughout the 30-minute postinfusion protocol (p < 0.01 to p < 0.001), but right ventricular stroke work index was only reduced at 15 minutes after infusion (p < 0.05) (Table I). When left and right ventricular stroke work indexes were plotted as functions of left and right filling pressure, respectively, both plots shifted downward at the time when the maximal extent of decrease in left and right ventricular stroke work index appeared (Figure 4, A and B).

DISCUSSION

Our data are consistent with those of Rocha et al³ who reported that right atrial, right ventricular and pulmonary pressures, and pulmonary vascular resistance did not change significantly after administration of 5 mg of intravenous nicardipine in patients with coronary

FIGURE 2. Correlation between the magnitude of decrease (%) in systemic vascular resistance (Δ SVR) and in pulmonary arteriolar resistance (Δ PAR) after intravenous infusion of nicardipine. n.s. = not significant.



artery disease (mean left ventricular end-diastolic pressure 19 ± 4 mm Hg), whereas mean aortic pressure decreased and systemic vascular resistance decreased significantly. Singh et al⁵ also observed that there was no significant change in either pressure or resistance in the pulmonary circulation, essentially reflecting a dominant afterload-reducing action with no significant venodilator effects during intravenous administration of nicardipine in patients with relatively normal ventricular function (mean pulmonary wedge pressure 9 ± 4 mm Hg). On the contrary, La Rovere et al⁴ observed significant decreases in mean pulmonary artery and right atrial pressures, and significant reduction of pulmonary artery resistance after administration of 5 mg of intravenous nicardipine in patients with a previous myocardial infarction (mean pulmonary wedge pressure $18 \pm$

2 mm Hg). Our results were quite different from La Rovere's data in the response of intravenous nicardipine, possibly due to the different basal hemodynamic status or lower dose of nicardipine, or both.⁹

We used positive and negative dp/dt_{max} as indexes of left ventricular systolic and diastolic function, respectively. Positive dp/dt_{max} may be influenced by heart rate, preload and afterload.^{11,12} In the present study, heart rate and left ventricular end-diastolic pressure significantly changed, but the number of these changes was small. On the other hand negative dp/dt_{max} has been reported to be a more reproducible measure of the rate of relaxation than an exponential time constant of isovolumic pressure decrease,¹³ and is most closely related to the magnitude of the peak aortic systolic pressure and, to a lesser degree, to the magnitude of cardiac

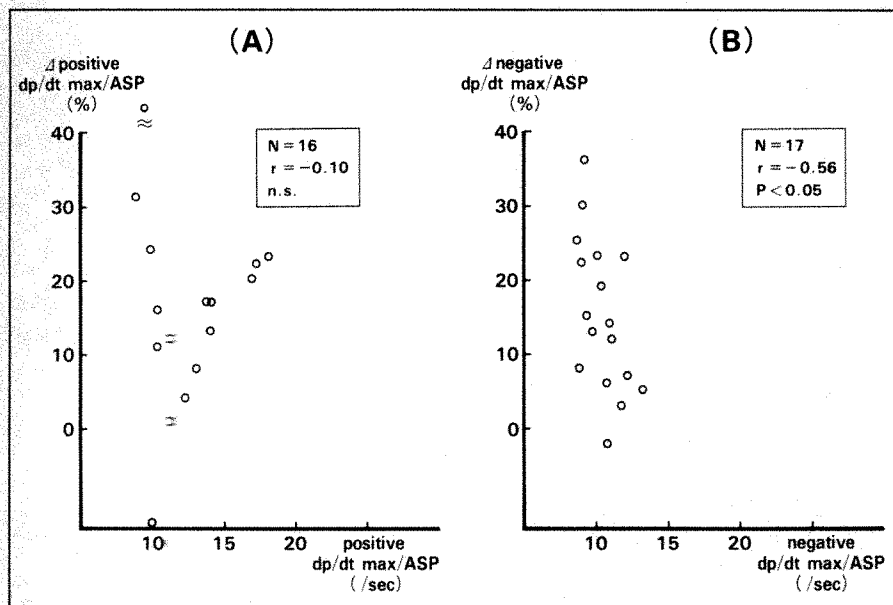


FIGURE 3. (A), correlation between positive maximal left ventricular pressure (dp/dt_{max}) and aortic systolic pressure (ASP) before intravenous infusion of nicardipine, and maximal extent of increase (%) in positive $dp/dt_{max}/ASP$ after infusion. (B), correlation between negative dp/dt_{max} and ASP before infusion, and maximal extent of increase in negative $dp/dt_{max}/ASP$ after infusion. $n.s.$ = not significant.

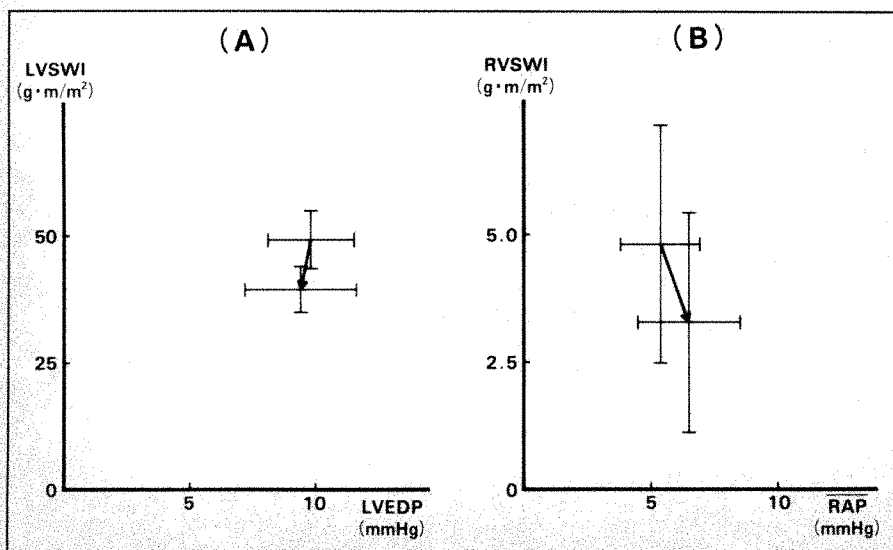


FIGURE 4. (A), left ventricular stroke work index (LVSWI) is plotted as a function of left ventricular end-diastolic pressure (LVEDP) before and after intravenous infusion of nicardipine. (B), right ventricular stroke work index (RVSWI) is plotted against mean right atrial pressure (RAP) before and after infusion.

output.^{12,14} Therefore, in the present study, positive and negative dP/dt_{max} were adjusted for aortic systolic pressure to correct the influences of afterload on left ventricular function. The present study did not show a significant decrease in positive dP/dt_{max} /aortic systolic pressure, even with a concomitant reduction in left ventricular filling pressure. Therefore, our data indicated that intravenous nicardipine exerted no negative inotropic effects on the left ventricle in our patients. However, the decrease in negative dP/dt_{max} , resulting largely from the decrease in aortic systolic pressure, and a significant inverse correlation between negative dP/dt_{max} /aortic systolic pressure before infusion and its maximal percent increase afterward, indicated that intravenous nicardipine had a beneficial effect on diastolic relaxation only in patients with impaired diastolic function. Satoh et al⁶ reported a dose-dependent decrease in developed tension of papillary muscles using isolated preparation, whereas Takenaka⁸ stated that intravenous nicardipine produced a positive inotropic effect with a low dose (1 to 10 $\mu\text{g/kg}$) and a negative inotropic effect with a high dose (0.1 to 1.0 mg/kg). Therefore, direct negative inotropic effects with a low dose of nicardipine can be masked in the intact circulation by the concomitant afterload reduction or by a reflex increase in sympathetic activity, or both. Pouleur et al² reported that intravenous nicardipine (2.5 mg) administered after propranolol (0.1 mg/kg) improved left ventricular pump function, had no negative inotropic effects and ameliorated left ventricular diastolic function in patients with coronary artery disease (mean left ventricular end-diastolic pressure 18 ± 5 mm Hg). Furthermore, they stated that the fact that its beneficial effect on diastolic function was still evident after propranolol indicated that this amelioration was not related to the reflex increase in sympathetic activity, but rather to the afterload reduction or to some other but still hypothetical metabolic effect. Our data indicated the depression of left ventricular pump function, probably due to the lower level of left ventricular end-diastolic pressure. Cohn et al¹⁵ reported that if cardiac func-

tion is normal or only slightly impaired, preload reduction has a greater effect than impedance reduction, and the net effect is a decrease in cardiac output.

In conclusion, a low dose (10 $\mu\text{g/kg}$) of intravenous nicardipine exerts a favorable effect on impaired diastolic function, but depresses left ventricular pump function with less marked effects on right heart circulation.

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Comparative Efficacy and Safety of Bepridil and Diltiazem in Chronic Stable Angina Pectoris Refractory to Diltiazem

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The efficacy and safety of bepridil hydrochloride (200 to 400 mg/day) were evaluated in patients with chronic stable angina refractory to maximal tolerated doses of diltiazem (median 360 mg/day) in a randomized, multicenter, double-blind, parallel study. Baseline diltiazem data were obtained during a 2-week period, after which 86 patients were randomized to bepridil (n = 46) or diltiazem (n = 40). Angina frequency, nitroglycerin consumption and ischemic manifestations induced by exercise treadmill testing were evaluated over 8 weeks. Bepridil significantly ($p < 0.05$) increased time to angina onset, time to 1 and 2 mm of ST-segment depression, total exercise time and total work over baseline values. Changes in time to angina onset and time to 1 mm of ST-segment depression were significantly ($p < 0.05$) greater for bepridil than for diltiazem. Angina frequency and nitroglycerin consumption did not differ significantly between groups. Compared with baseline, bepridil significantly ($p < 0.001$) decreased heart rate (mean 4 beats/min) and prolonged QTc (mean 35 ms). The most frequent adverse effects in both groups were nausea, asthenia, dizziness, headache and diarrhea. Four patients taking bepridil and 1 taking diltiazem withdrew from the study because of adverse reactions. No sudden deaths, myocardial infarctions or instances of sustained ventricular tachycardia or torsades de pointes occurred in either group. The data indicate that bepridil provided safe and effective antianginal and antiischemic therapy in patients with chronic

stable angina who exhibited less than optimal response to maximal tolerated doses of diltiazem.
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As a class of therapeutic agents, calcium antagonists have an established role in the treatment of many cardiovascular conditions,¹⁻¹⁰ including ischemic heart disease. However, not every calcium antagonist has a use for every indication because these drugs exhibit a wide spectrum of pharmacologic and pharmacokinetic properties,¹¹ particularly with respect to their effects on heart rate, their plasma elimination half-life and their hemodynamic effects. As with verapamil hydrochloride and diltiazem hydrochloride,¹²⁻¹⁴ bepridil hydrochloride exhibits a therapeutically significant sympatholytic action. This produces a statistically significant decrease in heart rate which may contribute to its antiischemic actions. Unlike verapamil and diltiazem, however, bepridil has a long plasma half-life, thus permitting once-daily administration. Bepridil also differs from these agents in that it increases the atrial and ventricular effective refractory periods and consequently prolongs the QTc interval.^{8,12-14}

Numerous trials have established the antianginal efficacy of once-daily doses of 200 to 400 mg of bepridil in chronic stable angina pectoris.¹⁵⁻²² However, the potential benefit of using bepridil when other calcium antagonists have provided suboptimal therapy is a topic that warrants further investigation. The objective of the present study was to compare the efficacy and safety of bepridil and diltiazem in patients with chronic stable angina refractory to maximal tolerated doses of diltiazem.

METHODS

Study design: This multicenter study used a double-blind, parallel design with randomization (block size 4) stratified by clinical site; 15 centers participated (see Appendix) and 86 patients entered the double-blind phase. The details of the study design are shown in Figure 1. At the first visit, baseline data were obtained and patients continued their currently prescribed regimen of

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diltiazem for 2 weeks. Study eligibility was determined at the second visit, and patients who were to enter the 8-week double-blind trial were randomly assigned either to continue receiving diltiazem, at the dose level previously established for them, or to receive bepridil. Diltiazem was discontinued for 24 hours before study medication was started. The study protocol was approved by the respective institutional review boards; all patients gave informed consent.

Patient selection: The study population consisted of patients with chronic stable angina pectoris refractory to a range of antianginal therapy. Specifically, immediately before the study they had received diltiazem at the maximal tolerated dose (not to exceed 360 mg/day) but had not demonstrated optimal therapeutic response, continuing to experience symptoms that interfered with the quality of their life, work or recreational activities. Patients who could tolerate β blockers, and in whom they were not contraindicated, had received them concomitantly with diltiazem, but this addition had not provided adequate therapy. The average angina attack rate for the group entering the double-blind phase was 8 per week per patient. Concomitant drug therapy was not altered during this phase.

During the evaluation period before the study, the diagnosis of chronic stable angina pectoris was confirmed by history and positive exercise tolerance test. The test was considered positive for ischemia if typical angina developed during exercise and was associated with ≥ 1.0 mm horizontal or downsloping ST-segment depression measured 0.08 second from the J point. All patients had resting electrocardiographic ST- and T-wave patterns that would not interfere with the correct interpretation of ST-segment deviation during subsequent exercise stress tests.

Patients who had experienced a myocardial infarction within 3 months of the study or had congestive heart failure or any other cardiac condition that might interfere with data interpretation or that would put them at undue risk were excluded from the study. Patients with bradycardia < 50 beats/min, those with QTc prolongation $> 15\%$ above the upper limit for their age or sex and those with serum potassium levels < 3.5 mEq/liter also were excluded.

Long-acting nitrates and β blockers were permitted and maintained at previously established fixed doses. Sublingual nitroglycerin was permitted for the relief of angina; however, prophylactic use of nitroglycerin was prohibited. Concomitant medications that would not interfere with the interpretation of study results were permitted. These included minor tranquilizers, nonnarcotic analgesic and diuretic drugs. Calcium antagonists other than the study drugs, antiarrhythmic drugs, cardiac

glycosides, tricyclic antidepressants and neuroleptics were not permitted.

Drug dosage and administration: Because diltiazem had been titrated in all patients to the highest permissible or tolerable level, dosage in the diltiazem group remained fixed at that level for the 8-week study period. The initial dosage for those randomized to receive bepridil was 200 mg once a day. Upward titration of bepridil was permitted in order to obtain optimal therapeutic response: Dosage could be increased at week 2 to 300 mg and at week 4 to 400 mg, the maximal allowable dose. If significant adverse reaction or QTc prolongation occurred, the dose was reduced.

Evaluation of efficacy: Patients encouraged to maintain their usual level of activities were given diaries in which to record frequency of angina attacks and number of nitroglycerin tablets taken. Diaries were reviewed by investigators at each visit (weeks 2, 4, 6 and 8). At the final visit, whenever it occurred, patients and investigators evaluated the response to therapy and compared the study medication with the previous diltiazem therapy.

Exercise tolerance tests were performed before the study, at entry into the double-blind therapy and at weeks 4 and 8. Treadmill exercise testing, using the Bruce protocol modified to include a stage $\frac{1}{2}$ at the outset, was performed at approximately the same time of the day for a given patient. To ensure that adequate levels of diltiazem were potentially available, the drug was administered 2 to 4 hours before the exercise tolerance test. Time to angina (the primary efficacy param-

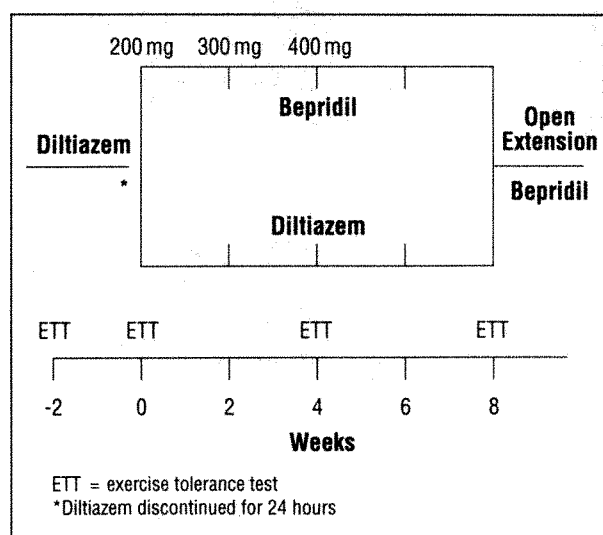


FIGURE 1. Protocol design of the multicenter double-blind study to determine the efficacy and safety of bepridil in patients refractory to maximal tolerated doses of diltiazem. The dosage of bepridil could be increased to 300 mg/day at week 2 and to 400 mg/day at week 4 to obtain optimal therapeutic response.

TABLE I Characteristics of Patients Studied

Parameters	Bepridil (n = 46)	Diltiazem (n = 40)
Sex		
Male	39	31
Female	7	9
Race		
White	38	37
Black	6	2
Other	2	1
Age (yr)		
Mean	62	62
Range	42-78	43-79
Weight (lb)		
Mean	184	180
Range	102-253	128-280

eter), total exercise time, time to 1 and 2 mm of ST-segment depression and total work were measured. If there was no angina or 1 or 2 mm of ST depression during exercise, total exercise time was substituted in the data analysis.

Work capacity in kilopond meters (kpm) was calculated from the results of each stage of the stress test, using the following formula: work (kpm) = $\sin \beta \times$ exercise time (seconds) \times body weight (kilograms) \times treadmill speed (meters/second) where β is the angle of inclination of the treadmill or $\beta = \arctan$ (treadmill grade in percent/100). Total work was computed as the sum of work done at each stage; this value was divided by 1,000.

Heart rate and blood pressure were recorded before and after exercise, at onset of angina and at 1, 3, 5 and 8 minutes after exercise. The type of ST-segment depression was recorded before and immediately after exercise. If the maximal ST-segment change occurred during the 8 minutes after cessation of exercise, the degree of ST-segment depression and the time after exercise to that depression were recorded.

Evaluation of safety: Heart rate, blood pressure and electrocardiograms were recorded at each visit. Clinical laboratory tests (hematology, serum chemistry and urinalysis) were performed at study entry and at weeks 4 and 8. Reports of adverse reactions were evaluated to determine their relationship to study drug.

Statistical analysis: Continuous demographic variables were compared between groups using 2-way analysis of variance. Categorical variables were compared between groups using Fisher's exact test. Diary information was averaged between visits. For stress test variables, changes from baseline were evaluated using the paired *t* test and were compared between treatment groups using a 2-way analysis of variance on ranks with investigator and treatment group as factors. To avoid serious problems of imbalance in the analysis and also to avoid the loss of data from 13 patients, investigators with <2 patients per drug group were pooled and con-

sidered as 1 investigator. If a significant ($p < 0.10$) treatment/investigator interaction was found, data for individual investigators were examined. The investigator and patient global evaluations and subjective comparisons with baseline diltiazem therapy were analyzed using the Mantel-Haenszel technique. Only the initial and final values were compared for vital signs, electrocardiograms and laboratory test data. With the exception of treatment/investigator interactions, statistical significance was defined as $p \leq 0.05$. For the efficacy variables, testing the hypothesis that bepridil was more effective than diltiazem, all tests were 1-sided. For the safety variables, testing for a difference between drug groups, all tests were 2-sided. SAS type II sums of squares were used for all analyses of variance.

RESULTS

Eighty-six patients (46 in the bepridil group and 40 in the diltiazem group) participated in the double-blind segment of the study. Analysis showed no statistically significant between-group differences demographically (Table I) or with regard to patient history of coronary artery disease or present cardiac status (Table II).

Fifty percent of the bepridil group and 60% of the diltiazem group were receiving the maximal dose of diltiazem (360 mg/day) immediately before the study. Other doses of diltiazem ranged from 90 to 270 mg/day; the median dose was 360 mg/day. β Blockers, administered to 72% of the patients taking bepridil and to 58% of those taking diltiazem, were continued at the same dose, as were long-acting nitrates, which were used by 52% in the bepridil and 60% in the diltiazem groups. There were no significant between-group differences for any of these variables. During the study, the daily doses of bepridil ranged from 200 to 400 mg (median 300). Weeks 4 through 8 of the study represent therapy at the maximal dose for the patients receiving bepridil.

Of the 86 patients, 72 (37 receiving bepridil and 35 receiving diltiazem) completed the study. The reasons for discontinuing therapy prematurely were adverse experiences (4 [9%] bepridil, 1 [3%] diltiazem); increased angina (4 [9%] bepridil, 1 [3%] diltiazem); intercurrent illness (0 bepridil, 1 [3%] diltiazem); other (noncompliance, 1 [2%] bepridil; and administrative, 2 [5%] diltiazem). The adverse effects experienced by the bepridil patients were dizziness on day 1; lightheadedness and wide QRS interval at 28 days; left bundle-branch block at 28 days; and fever, leukopenia and pharyngitis at 55 days. The patient taking diltiazem withdrew on day 5 because of nonspecific chest pain. Symptoms in all of these patients resolved, either spontaneously or with additional therapy, when study drug was withdrawn.

Investigator-treatment interactions: A statistically significant ($p < 0.10$) investigator-treatment interaction

was found for 3 exercise tolerance parameters—total exercise time at week 4 ($p = 0.061$), total work at week 4 ($p = 0.065$), angina attack rate at baseline ($p = 0.023$) and final visit ($p = 0.065$)—and QTc at final visit ($p = 0.061$). When this interaction was analyzed, results from 1 investigator, whose patients represented 12% of the study population, were different from the other results. In this investigator's study, the condition of patients taking bepridil deteriorated on average, whereas that in patients taking diltiazem improved. The QTc interval of his bepridil patients did not change, whereas the QTc interval in those taking diltiazem increased. Although every effort was made to de-

termine if this investigator's population was different in some way that would account for the incongruous results, no explanation was found. Therefore, data from these patients are included in the results.

Measures of ischemia during treadmill exercise:

Mean values and mean changes for exercise tolerance test parameters (times to angina, 1 and 2 mm of ST-segment depression, total exercise time and total work) are displayed in Table III. Data from 5 bepridil patients and 4 diltiazem patients for whom either baseline or follow-up information was missing were excluded from analysis. Treatment with bepridil resulted in a statistically significant increase from baseline in all param-

TABLE II Baseline Cardiac Status by Study Group

	Bepridil			Diltiazem		
	No.	Mean	Range	No.	Mean	Range
Previous myocardial infarction*	46	0.9 ± 0.1	0-3	38†	0.9 ± 0.2	0-5
Vessels with >60% obstruction	36	2.1 ± 0.2	0-4	31	2.5 ± 0.2	0-4
Bypassed vessels‡	45§	0.5 ± 0.1	0-3	39§	0.7 ± 0.2	0-4
Left ventricular ejection fraction	28	60.2 ± 2.1	31-80	24	58.2 ± 2.4	32-81

*Twenty-eight of 46 patients taking bepridil and 20 of 40 patients taking diltiazem had history of myocardial infarction.
†Case records for 2 patients did not indicate number of myocardial infarctions.
‡Seventeen of 46 patients taking bepridil and 16 of 40 patients taking diltiazem had history of coronary artery bypass surgery.
§Case record for 1 patient did not indicate number of bypassed vessels.
Data not available for all patients. Values are mean \pm standard error of the mean.

TABLE III Effects of Bepridil and Diltiazem on Exercise Tolerance Test Parameters

	Bepridil				Diltiazem			
	No.	Mean	Mean Change	Difference from Baseline	No.	Mean	Mean Change	Difference from Baseline
Time to angina (min)								
Baseline	41	6.6 ± 0.5			36	6.1 ± 0.4		
Week 4	41	8.0 ± 0.6	1.4 ± 0.3	<0.001	36	6.8 ± 0.5	0.7 ± 0.4	NS
Week 8	36	8.7 ± 0.6	$1.8 \pm 0.4^{\dagger}$	<0.001	35	6.9 ± 0.4	0.8 ± 0.4	NS
Final*	41	8.4 ± 0.6	$1.8 \pm 0.4^{\dagger}$	<0.001	36	6.8 ± 0.4	0.7 ± 0.4	NS
Time to 1-mm ST Dep (min)								
Baseline	41	6.8 ± 0.5			36	6.6 ± 0.4		
Week 4	41	8.0 ± 0.5	$1.2 \pm 0.3^{\dagger}$	<0.001	36	6.4 ± 0.5	-0.2 ± 0.4	NS
Week 8	36	8.6 ± 0.6	$1.5 \pm 0.4^{\dagger}$	<0.001	35	7.0 ± 0.4	0.5 ± 0.3	NS
Final*	41	8.3 ± 0.5	$1.5 \pm 0.3^{\dagger}$	<0.001	36	7.0 ± 0.4	0.5 ± 0.3	NS
Time to 2-mm ST Dep (min)								
Baseline	41	8.2 ± 0.5			36	7.9 ± 0.4		
Week 4	41	8.8 ± 0.5	0.6 ± 0.2	<0.05	36	8.1 ± 0.4	0.2 ± 0.3	NS
Week 8	36	9.5 ± 0.5	0.8 ± 0.3	<0.01	35	8.2 ± 0.4	0.3 ± 0.3	NS
Final*	41	9.1 ± 0.5	0.9 ± 0.3	<0.01	36	8.2 ± 0.4	0.3 ± 0.3	NS
Total exercise time (min)								
Baseline	41	8.6 ± 0.5			36	8.2 ± 0.4		
Week 4	41	9.0 ± 0.5	$0.5 \pm 0.2^{\dagger}$	NS	36	8.2 ± 0.4	0.0 ± 0.2	NS
Week 8	36	9.6 ± 0.5	0.5 ± 0.2	<0.05	35	8.3 ± 0.4	0.1 ± 0.3	NS
Final*	41	9.2 ± 0.5	0.6 ± 0.2	<0.05	36	8.3 ± 0.4	0.1 ± 0.3	NS
Total work (kpm/1,000)								
Baseline	41	4.0 ± 0.4			36	3.5 ± 0.3		
Week 4	41	4.4 ± 0.4	$0.4 \pm 0.2^{\dagger}$	NS	36	3.4 ± 0.3	-0.2 ± 0.2	NS
Week 8	36	4.9 ± 0.5	0.5 ± 0.2	<0.05	35	3.6 ± 0.4	0.1 ± 0.3	NS
Final*	41	4.6 ± 0.4	0.5 ± 0.2	<0.01	36	3.6 ± 0.4	0.1 ± 0.3	NS

*Patient's last visit, whenever it occurred.

†Significantly ($p < 0.05$) different from diltiazem mean change.

‡Significantly ($p < 0.01$) different from diltiazem mean change.

Values are mean \pm standard error of the mean.

Dep = depression; kpm = kilopond meters; NS = not significant.

TABLE IV Effects of Bepridil and Diltiazem on Resting Heart Rate and QTc Interval

	Bepridil				Diltiazem			
	No.	Mean	Mean Change	Difference from Baseline	No.	Mean	Mean Change	Difference from Baseline
Heart rate (beats/min)								
Baseline	45	60 ± 2			38	62 ± 2		
Week 4	37	57 ± 2	-4 ± 1 [†]	<0.001	31	64 ± 2	1 ± 2	NS
Week 8	36	55 ± 2	-5 ± 1	<0.001	34	62 ± 2	-1 ± 2	NS
Final*	45	56 ± 1	-4 ± 1	<0.001	38	61 ± 2	-1 ± 2	NS
QTc (ms)								
Baseline	45	415 ± 4			38	418 ± 4		
Week 4	37	452 ± 7	34 ± 6 [†]	<0.001	31	431 ± 6	8 ± 6	NS
Week 8	36	456 ± 6	40 ± 6 [†]	<0.001	34	421 ± 6	1 ± 7	NS
Final*	45	450 ± 6	35 ± 6 [†]	<0.001	38	419 ± 5	1 ± 6	NS

*Patient's last visit, whenever it occurred.

[†]Significantly ($P < 0.01$) different from diltiazem mean change.[‡]Significantly ($P < 0.001$) different from diltiazem mean change.

Values are mean ± standard of error of the mean.

NS = not significant.

eters at all evaluations except total exercise time and total work at week 4, with a trend toward continued improvement between weeks 4 and 8. Changes from baseline with diltiazem were not significant.

Angina frequency and nitroglycerin consumption:

Mean data are shown in Figures 2 and 3. In both groups, the number of angina attacks per week was reduced significantly starting at week 4; there were no significant between-group differences. Mean number of nitroglycerin tablets taken per week was reduced in both groups by week 8 of the study, and there were no significant differences between groups.

Rate-pressure product: Compared with baseline values, the final mean peak heart rate/systolic blood

pressure product tended to be significantly lowered with both bepridil (from 18.0 to 16.7) and diltiazem (from 18.7 to 17.4). However, the magnitude of this change was not significantly different between the 2 drugs.

Resting heart rate and QTc: Mean baseline data and mean changes at weeks 4 and 8 and at the final visit are listed in Table IV. Diltiazem produced no significant change from baseline in heart rate. Bepridil reduced mean heart rate by 4 beats/min from baseline to final visit. Mean change from baseline with bepridil was statistically significant ($p < 0.001$) at all evaluation points. However, the difference between the effects of bepridil and diltiazem was significant ($p < 0.01$) only at week 4. Bepridil prolonged the mean QTc interval from

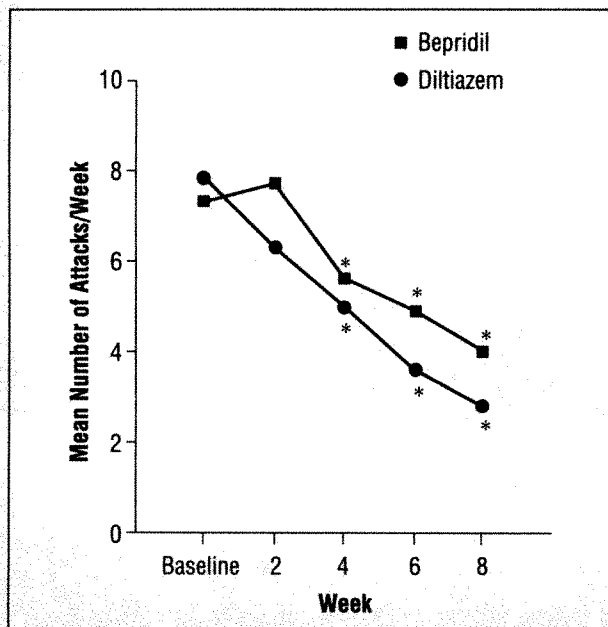


FIGURE 2. Comparative effects of bepridil and diltiazem on the mean number of weekly angina attacks. *Significant ($p < 0.05$) difference from baseline.

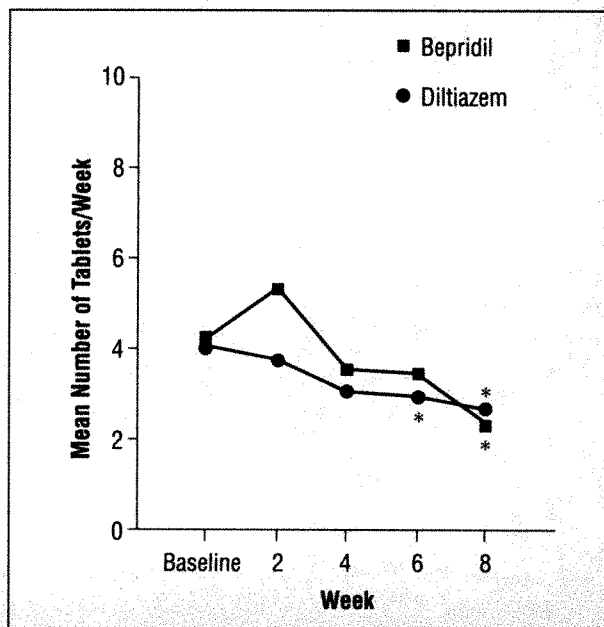


FIGURE 3. Comparative effects of bepridil and diltiazem on the mean number of nitroglycerin tablets consumed per week. *Significant ($p < 0.05$) difference from baseline.

baseline to the final visit by 35 ms. Mean change in QTc seen with bepridil was statistically significant not only compared with baseline ($p < 0.001$) but also compared with the mean diltiazem changes at each evaluation ($p \leq 0.003$).

Adverse experiences: Seventy-five percent of patients taking diltiazem and 87% taking bepridil reported adverse experiences. Most of these ($>55\%$) were mild. Incidences of the most frequently occurring adverse reactions are compared in Table V. Incidences of constipation and edema, adverse effects associated with other calcium antagonists, were 0 and 2% for bepridil and 5 and 8% for diltiazem. In terms of clinical laboratory results, 2 patients had minimal alterations of 1 or both transaminases and 1 patient, who discontinued therapy prematurely, had leukopenia. No sudden deaths or myocardial infarctions occurred in either group, nor were there any cases of sustained ventricular tachycardia or torsades de pointes.

DISCUSSION

Numerous multicenter and single investigator studies in patients with chronic stable angina have established that bepridil given once a day (200 to 400 mg/day) delays the onset of chest pain, increases the duration of exercise on the treadmill, delays ST-segment deviations, reduces angina frequency and nitroglycerin consumption and attenuates the electrocardiographic manifestations of ischemia induced by exercise.¹⁵⁻²²

Our study extends these observations to patients with chronic stable angina refractory to maximal tolerated doses of diltiazem. A major difference between our patients and those in the earlier trials, all but 2 of which prohibited concomitant use of β blockers, is that more than half of our patients required β blockers and long-acting nitrates and were maintained on their pre-study doses while they were receiving study medication. Although no direct comparisons were made with patient populations in other trials, this indirect comparison may indicate that patients in our study had more serious cardiovascular disease than did patients in the earlier trials.

This study was designed to show that, with respect to symptomatic relief of angina, if patients are resistant to diltiazem, treatment with bepridil offers benefits over continuing with diltiazem. To qualify, patients had to be experiencing symptoms that interfered with their quality of life despite the fact that they were taking maximal tolerated doses of diltiazem. Therefore, the lack of change from baseline in patients randomized to diltiazem is consistent with the fact that their baseline values already represented their best possible response to diltiazem. A number of comparative tests were made between treatment groups; the consistency of the results

TABLE V Most Frequently Occurring Adverse Effects During Double-Blind Therapy

	Number (%) of Patients	
	Bepridil (n = 46)	Diltiazem (n = 40)
Nausea	10 (22%)	3 (8%)
Asthenia	8 (17%)	4 (10%)
Dizziness	8 (17%)	2 (5%)
Headache	7 (15%)	3 (8%)
Diarrhea	7 (15%)	1 (3%)

indicated that, when substituted for diltiazem, bepridil provided additional efficacy in these patients who were not experiencing a satisfactory response to diltiazem.

The investigator-treatment interactions observed for the exercise tolerance test parameters of total exercise time and total work at week 4 were of interest. Since the cause of the interactions could not be ascertained, we chose to be statistically conservative and to present the results with the contradictory data included. Had these data been excluded from analysis, the comparisons between treatment groups with regard to stress test results would have favored the bepridil group much more strongly. Even with our approach, mean changes from baseline to final visit for time to angina onset and time to 1 mm of ST-segment depression were significantly greater with bepridil than with diltiazem.

The mechanisms underlying the possible differences between the effects of bepridil and diltiazem on the parameters of ischemia induced by exercise stress testing are not certain. In this study, bepridil appeared to exert a slightly greater bradycardic effect associated with a correspondingly lower rate-pressure product. However, although not statistically significant, a higher percentage of the bepridil patients (72 vs 58% for diltiazem) were receiving concurrent β -blocker therapy. With bepridil, the beneficial antiischemic effects as determined by stress testing tended to increase as a function of time; such a trend was not discernible with diltiazem.

In light of the study design, it is not surprising that fewer patients in the diltiazem group than in the bepridil group discontinued therapy prematurely because of increased angina. The long half-life of bepridil may also help explain this result: 2 of the patients taking bepridil took the drug for <1 week, and their plasma drug levels may not have reached steady state before the patients withdrew from the trial. Likewise, perhaps because the study design effectively eliminated patients whose therapeutic response to diltiazem would have been totally outweighed by adverse experiences, the overall incidence of adverse experiences was less in the diltiazem than in the bepridil group.

In accordance with the data in animal preparations in which bepridil²³ lengthened repolarization, the drug prolonged the QTc interval in other clinical studies^{24,25}

as it did in the current study by a mean of 35 ms. This effect was evident by week 4 and did not appear to increase with time. There were no instances of torsades de pointes or sudden death.

In conclusion, the present study documents the safety and efficacy of once-daily doses of bepridil in patients with chronic stable angina pectoris refractory to maximal tolerated doses of diltiazem. Whereas these results cannot be used to imply that bepridil would be more effective than diltiazem in all patients with chronic stable angina, they do provide objective evidence in our subgroup of patients for the benefit of bepridil as an alternative to continuing with diltiazem when it failed to provide optimal control of angina.

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APPENDIX

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Safety and Efficacy of Percutaneous Transluminal Coronary Angioplasty in Patients with Left Ventricular Dysfunction

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The risks and long-term outcome after 845 elective percutaneous transluminal coronary angioplasties (PTCA) in patients with left ventricular (LV) dysfunction (ejection fraction $\leq 40\%$) were examined. Procedural results were compared with 8,117 consecutive procedures in patients with ejection fractions $>40\%$. The patients with LV dysfunction were older (63 vs 60 years, $p < 0.01$), had a greater incidence of prior myocardial infarction (84 vs 45%, $p < 0.001$), prior bypass surgery (39 vs 21%, $p < 0.001$), 3-vessel disease (62 vs 33%, $p < 0.001$), and class IV angina (48 vs 41%, $p < 0.01$) than the control group. Angiographic success was lower (93 vs 95%, $p < 0.01$), and overall procedural mortality was increased (4 vs 1%, $p < 0.001$) in the study group. Emergency surgery rates were identical (2%). No significant difference was found in rates of nonfatal Q-wave myocardial infarction (2 vs 1%). At mean follow-up of 33.5 months, 15% of the patients with LV dysfunction required late bypass surgery, 27% underwent repeat PTCA, and 59% were angina free. Actuarial survival at 1 and 4 years was 87 and 69%, respectively. Cox regression analysis identified 3-vessel disease, age ≥ 70 years, class IV angina and incomplete revascularization as correlates of long-term mortality. These data suggest that PTCA may be an effective treatment for coronary artery disease in patients with LV dysfunction.

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After the introduction of percutaneous transluminal coronary angioplasty (PTCA) as a non-operative method of myocardial revascularization, it was estimated that only about 5% of patients with coronary artery disease would be candidates for the procedure.¹ Patients with left ventricular (LV) dysfunction were considered to be poor candidates for PTCA. Over the past decade advances in operator experience and improved equipment have greatly expanded the range of patients with coronary artery disease potentially suitable for treatment with PTCA.² The discouraging natural history of medically treated patients with LV dysfunction,^{3,4} combined with the increased risks of surgical revascularization in these patients,^{5,6} provided the impetus to consider PTCA as a therapeutic option in these patients. Only limited experiences with PTCA in patients with LV dysfunction are available.⁷⁻¹⁰ The present study examines the procedural risks and long-term outcome after PTCA in a large group of patients with LV dysfunction.

METHODS

Patient population: Beginning in 1980, clinical and procedural details of patients undergoing PTCA by our group have been prospectively recorded and entered into a computerized database. Many patients were referred from outside institutions and had diagnostic catheterization studies performed at other centers. Patients with an ejection fraction $\leq 40\%$, calculated from contrast ventriculography at our institution or at an outside hospital, were coded as LV dysfunction. Ejection fractions were calculated from ventriculograms performed in the right anterior oblique projection using the Kennedy regression equation.¹¹ Referral catheterization films that were not accompanied by a calculated ejection fraction were reviewed at the time of receipt by an experienced invasive cardiologist and a visual assessment of LV ejection fraction as $>40\%$ or $\leq 40\%$ was made before PTCA. The hospital and clinic charts of every patient with a visually estimated ejection fraction $\leq 40\%$ were reviewed in detail and patients were included in the study only if additional evidence of poor LV

function (i.e., radionuclide or echocardiographic studies) was available.

Angioplasty protocol: Surgical standby was available at all times, although in a few carefully selected patients with end-stage ventricular dysfunction or concomitant critical medical conditions, or both, it was understood by the patient and family before the procedure that emergency surgical intervention was not reasonable. Unless contraindicated, routine premedications included 325 mg of aspirin 1 to 3 times daily, dipyridamole 75 mg 3 times daily, isosorbide dinitrate 5 mg sublingually, lidocaine intravenously 75 mg, and a calcium antagonist. After arterial access, 10,000 U of heparin were administered intravenously and an additional 5,000 U were given for each additional hour of the procedure. Typically, 3 to 5 inflations lasting 45 to 90 seconds were performed across each lesion using pressure sufficient to achieve full balloon expansion. Shorter balloon inflations were used if severe angina pectoris or important hypotension occurred. Aortic pressure was monitored continuously from the guide catheter. In selected cases, an intraaortic balloon pump was inserted at either the beginning of the procedure or during the procedure to provide hemodynamic support. This decision was made by the individual operator and was not outlined by protocol. Percutaneous cardiopulmonary bypass support was not used in any patients in this series. After the procedure, sheaths were kept in place for 24 hours while a heparin infusion was adjusted to maintain the partial thromboplastin time at 2 to 3 times control. At discharge, patients continued to take aspirin and a calcium antagonist in addition to other medicines as needed.

Study definitions: Significant coronary artery stenoses were considered to be luminal diameter narrowings of $\geq 70\%$ estimated visually. Multilesion PTCA was defined as an attempt to dilate ≥ 2 stenoses occurring in the same or different arteries. Multivessel PTCA was defined as an attempt to dilate ≥ 2 stenoses that were in different epicardial coronary arterial systems. Angiographically successful PTCA was defined as a reduction in luminal diameter narrowing to $\leq 40\%$ as determined by the operator. Clinically successful PTCA was defined as angiographic success in all sites attempted without complicating myocardial infarction, urgent coronary artery bypass grafting or death. A myocardial infarction was defined by the presence of typical prolonged chest pain accompanied by new Q waves on the electrocardiogram and an increase in creatine kinase and MB isoenzymes. Creatine kinase levels were not routinely measured after uncomplicated PTCA. All hospital deaths were reviewed by a single physician not participating in the PTCA procedures. Procedural death was defined as a death occurring any time during the patient's hospitalization due directly to the PTCA

or arising from late PTCA complications (e.g., contrast induced renal failure). Total hospital mortality also included noncardiac deaths before hospital discharge resulting from associated medical diseases or cardiac deaths due to preexisting disease not attributable to the PTCA. Complete revascularization with PTCA was defined as no remaining residual stenoses in epicardial arteries or bypass grafts $\geq 50\%$ after dilatation, including chronic total occlusions. Event-free survival was defined as freedom from death, nonfatal myocardial infarction, and coronary artery bypass grafting in follow-up.

Predicted mortality: To characterize the mortal risk of PTCA in these patients compared with surgical revascularization, the most recent 100 patients in this series with a calculated ejection fraction $\leq 40\%$ and without prior coronary artery bypass surgery were reviewed. Their contrast ventriculograms were reviewed by a single experienced angiographer without knowledge of the patient identity, characteristics or procedural outcome. Regional wall motion was assessed in the right anterior oblique projection and was graded according to the scoring system of the Coronary Artery Surgery Study on a scale of 5 to 30.^{12,13} A predicted operative mortality for elective coronary artery bypass grafting was calculated for each patient by the Coronary Artery Surgery Study,^{12,13} using the revised coefficients of Fisher and Kennedy.¹⁴

Follow-up: The status of hospital survivors was ascertained by outpatient follow-up or questionnaires through the mail regarding subsequent cardiac procedures or events. Nonresponders were questioned over the telephone whenever possible.

Statistics: All continuous data are presented as mean \pm 1 standard deviation. The 2 tailed Student *t* test or Fisher's exact test was used for comparison of continuous variables and the chi-square test was used for categorical variables. Survival curves were generated using the Kaplan-Meier actuarial method, and comparisons between survival distributions were made using the Lee-Desu statistic. Stepwise logistic regression was used to evaluate the effect of selected clinical variables on in-hospital mortality. A Cox proportional-hazards model was used to evaluate long-term survival after PTCA. A *p* value < 0.05 was considered significant.

RESULTS

Patient characteristics: During the study period (1980 to 1989), 8,962 PTCA procedures were performed for indications other than acute myocardial infarction. LV dysfunction (ejection fraction $\leq 40\%$) was present in 704 patients undergoing 845 procedures (9.4%), constituting the study group. The clinical and angiographic features of the patients undergoing these procedures are listed in Table I and are compared with

the 8,117 procedures performed during the same period in patients with ejection fractions $>40\%$. Overall, the patients with LV dysfunction were older, more likely to have had a prior myocardial infarction or diabetes mellitus, presented more often with severe angina, and had more extensive coronary artery disease. In 507 (60%) of the procedures in patients with LV dysfunction, a calculated ejection fraction was available from contrast left ventriculography. In the other 338 procedures, the estimated ejection fraction, corroborated by a detailed chart review, was $\leq 40\%$, but a precise value was not assigned. When the clinical characteristics and major procedural outcomes of the patients with calculated and estimated ejection fractions were compared, there were no consistent differences between the 2 groups to suggest selection biases (Table II). Therefore, unless indicated otherwise, the results were analyzed for all 845

procedures. Among the 507 procedures in patients with a calculated ejection fraction $\leq 40\%$, mean ejection fraction was $31 \pm 7\%$ (range of 10 to 40). Ejection fraction was 30 to 40% in 331 of the procedures (65%), 20 to 29% in 145 procedures (29%), and $<20\%$ in 31 procedures (6%).

Angioplasty results: The results of PTCA in patients with and without LV dysfunction are summarized in Table III. During the 845 procedures in patients with ejection fractions $\leq 40\%$, PTCA was attempted in 2,211 lesions (2.6 per procedure). Angiographic success was achieved in 2,065 lesions (93%), which was lower than the success in 18,149 of 19,132 lesions (95%) in patients with ejection fractions $>40\%$ ($p = 0.007$). The number of stenoses dilated ranged from 1 to 15. Multivessel PTCA was performed in 377 procedures (45%). An intraaortic balloon pump was

TABLE I Clinical and Angiographic Baseline Characteristics of Patients with Left Ventricular Ejection Fractions (LVEF) $\leq 40\%$ Compared with $> 40\%$ Treated with Percutaneous Transluminal Coronary Angioplasty

	LVEF $\leq 40\%$	LVEF $> 40\%$	p Value
Procedure no.	845	8,117	
Mean age (yr)/range	63/26–89	60/15–92	<0.01
Age > 70 years (%)	236 (28)	1,581 (20)	<0.001
Men (%)	665 (79)	6,310 (78)	0.53
Prior myocardial infarction (%)	713 (84)	3,490 (45)	<0.001
Prior coronary bypass (%)	333 (39)	1,736 (21)	<0.001
Diabetes mellitus (%)	208 (25)	1,108 (14)	<0.001
NYHA angina class			
I–II (%)	279 (33)	2,871 (37)	
III (%)	161 (19)	1,755 (22)	
IV (%)	405 (48)	3,175 (41)	<0.001
1-vessel disease (%)	86 (10)	2,631 (32)	
2-vessel disease (%)	233 (28)	2,840 (35)	
3-vessel disease (%)	526 (62)	2,646 (33)	<0.001
Left main disease (%)	38 (5)	123 (2)	<0.001

NYHA = New York Heart Association.

TABLE II Comparison of Clinical and Angioplasty Procedural Variables in Patients with Calculated or Estimated Ejection Fractions $\leq 40\%$

	Calculated EF $\leq 40\%$	Estimated EF $\leq 40\%$	p Value
Procedure no. (%)	507 (60)	338 (40)	
Mean age (yr)	63 ± 10	62 ± 10	0.91
Age ≥ 70 years (%)	146 (29)	90 (27)	0.54
Men (%)	396 (78)	269 (80)	0.61
Prior myocardial infarction (%)	440 (87)	273 (81)	0.02
Prior coronary bypass (%)	166 (33)	167 (49)	<0.001
NYHA angina class			
I–II (%)	182 (36)	97 (29)	
III (%)	86 (17)	75 (22)	
IV (%)	239 (47)	166 (49)	0.06
No. of coronary arteries narrowed $\geq 70\%$ in diameter			
1 (%)	61 (12)	25 (7)	
2 (%)	149 (29)	84 (25)	
3 (%)	297 (59)	229 (68)	0.01
Left main disease $\geq 50\%$ (%)	18 (4)	20 (6)	0.10
Procedural infarction (%)	11 (2)	4 (1)	0.29
Urgent coronary bypass (%)	10 (2)	8 (2)	0.70
Intraaortic balloon (%)	72 (14)	41 (12)	0.69
Procedural death (%)	23 (4)	12 (4)	0.48
Hospital stay (days)	5 ± 4	4 ± 5	0.68

EF = ejection fraction; NYHA = New York Heart Association.

TABLE III Comparison of Procedural Results and Complications of Percutaneous Transluminal Coronary Angioplasty in Patients with Left Ventricular Ejection Fractions \leq or $>$ 40%

	LVEF \leq 40%	LVEF $>$ 40%	p Value
Procedure number	845	8,117	
Lesions attempted	2,211	19,132	
Stenoses dilated/procedure	2.6 \pm 1.8	2.4 \pm 1.6	0.54
Multilesion angioplasty (%)	564 (67)	5,011 (62)	0.005
Multivessel angioplasty (%)	377 (45)	3,378 (42)	0.10
Angiographic success (%)	2,065 (93)	18,149 (95)	0.007
Clinical success (%)	683 (81)	7,094 (87)	$<$ 0.001
Complete revascularization (%)	249 (29)	4,819 (59)	$<$ 0.001
Urgent bypass surgery (%)	18 (2)	129 (2)	0.30
Nonfatal infarction (%)	15 (2)	115 (1)	0.41
Procedural death (%)	35 (4)	53 (1)	$<$ 0.001
Total hospital death (%)	42 (5)	70 (1)	$<$ 0.001
Length of hospital stay (days)	4.4	3.5	0.70

LVEF = left ventricular ejection fraction.

used in conjunction with PTCA in 113 procedures (13%). In 76 procedures, the balloon pump was placed prophylactically for hemodynamic support during the procedure. Among the 507 procedures in patients with calculated ejection fractions, prophylactic balloon pump support was used 6% of the time with an ejection fraction of 30 to 40%, 14% of the time with an ejection fraction of 20 to 29%, and 29% of the time with an ejection fraction $<$ 20%. In the remaining 37 procedures the balloon pump was placed emergently during the procedure for severe hemodynamic instability or vessel closure. Complete revascularization was achieved with PTCA in 249 procedures (29%). Mean length of hospital admission was 4.4 days for patients with LV dysfunction compared with 3.5 days for patients with preserved function ($p = 0.7$).

Procedural complications: A comparison of procedural complications in patients with and without LV dysfunction is presented in Table III. In patients with LV dysfunction, procedural complications of urgent bypass surgery, Q-wave myocardial infarction or death occurred after 53 procedures (6%). Urgent bypass surgery was performed in 18 patients (2%) for acute vessel closure, 6 of whom died in hospital. A nonfatal Q-wave myocardial infarction after PTCA occurred in 15 patients (2%). Procedural death complicated PTCA in 35 patients (4%). The yearly death rate from 1980 to 1989 ranged from 0 to 11%, and was \leq 3% in each of the years 1987 to 1989. The most frequent cause of procedural death was vessel closure in 27 procedures. Six of these patients were treated with emergency bypass surgery but could not be weaned off of cardiopulmonary bypass. Nine patients with acute vessel closure in the catheterization laboratory and 12 patients who occluded a vessel after transfer out of the laboratory died before transfer for surgery or repeat PTCA. Five additional patients died of contrast nephropathy and 3 patients of congestive heart failure. Procedural death occurred in 14 of 331 procedures in patients with an

ejection fraction of 30 to 40% (4%), in 7 of 145 procedures with an ejection fraction of 20 to 29% (5%), and in 2 of 31 procedures with an ejection fraction $<$ 20% (6%) ($p = 0.8$).

Hospital mortality: An additional 7 patients died before discharge for a total hospital mortality rate of 5%. In 5 patients, unsuccessful but uncomplicated PTCA led to referral for elective coronary bypass grafting. Death occurred in 4 patients from 1 to 4 days postoperatively due to a low cardiac output syndrome and in 1 patient from a massive cerebral air embolus. One patient died of a massive stroke 16 days after PTCA while undergoing cardiac rehabilitation. One patient with recurrent ventricular arrhythmias before PTCA died of ventricular fibrillation 5 days after successful PTCA despite documentation of persistent arterial patency at the dilatation site. Logistic regression analysis identified age \geq 70 years and the presence of New York Heart Association class IV angina as independent predictors of hospital mortality.

Predicted operative mortality: The predicted operative mortality for coronary artery bypass grafting in the most recent 100 patients using the Coronary Artery Surgery Study formula¹²⁻¹⁴ was 10.3%. Furthermore, 41 of the 100 patients were prospectively coded by the dilating physician to be relatively or absolutely inoperable due to severe ventricular dysfunction, diffuse coronary disease, absent surgical conduit or advanced medical conditions. The observed PTCA procedural mortality for these 100 patients was 3% ($p = 0.08$ compared with the predicted operative mortality).

Long-term results: At hospital discharge, 662 patients were alive. The time from the PTCA procedure to the time of follow-up was $<$ 6 months in 34 patients, all of whom were alive and well. Six patients $>$ 6 months from their PTCA were lost to follow-up. Therefore, 622 of the 628 patients (99%) \geq 6 months (mean 33 ± 24) from their PTCA were available for follow-up.

During follow-up there were 161 late deaths. Overall survival and event-free survival are demonstrated in Figure 1. The actuarial 1- and 4-year survival rates were 87 and 69%, respectively. Event-free survival rates at 1 and 4 years were 71 and 47%, respectively. Cox multivariate analysis identified age >70 years, the number of diseased vessels and class IV angina as independently related to long-term mortality.

Late coronary bypass grafting was performed in 92 patients (15%) and a late nonfatal myocardial infarction occurred in 50 patients (8%). At follow-up, class I angina was reported in 280 patients, class II angina in 96 patients, class III angina in 68 patients and class IV angina in 27 patients. No further PTCA procedures were performed in 458 of the 632 patients (73%) followed. Repeat PTCA was performed in 174 patients (27%).

DISCUSSION

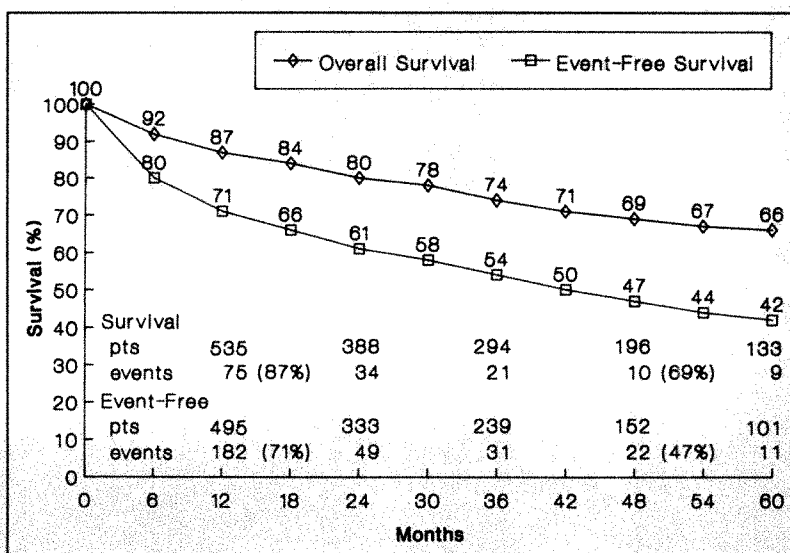
An attempt to examine any subgroup of patients for risks and outcome is hampered by the frequent presence of additional factors potentially influencing procedural results. The study patients in this report not only had worse LV function than the control group, but also were older, and had more extensive coronary artery disease, advanced angina pectoris and diabetes mellitus. Patients were frequently specifically referred from outside institutions for refractory symptoms, unfavorable anatomy or complicated medical conditions.

The angiographic success of the lesions attempted was high (93%) but less than in patients with relatively preserved LV function. The technique of PTCA is often more challenging in patients with poor LV function. Shorter balloon inflations may be required due to less tolerance for transient ischemia. Guide catheter position must be monitored vigilantly to avoid prolonged obstruction to flow. Less tolerance for vasodilators

administered routinely for the procedure may occur. Smaller volumes of contrast media may be required to avoid pulmonary edema. Although the number of stenoses attempted was similar in patients with LV dysfunction as in patients with relatively preserved function, the extent of coronary artery disease was greater in the group with LV dysfunction. Therefore, complete revascularization was achieved less frequently with PTCA in patients with LV dysfunction. Because a strategy of dilating all lesions supplying ischemic myocardium was generally used, the incomplete revascularization resulted predominantly from chronically occluded native coronary arteries and grafts that either could not be opened or were not attempted due to unfavorable angiographic characteristics.¹⁵

Over a 10-year experience, the mortal procedural risk of PTCA was 4 times higher in patients with LV dysfunction. Procedural mortality was lower in the last 3 years, and was $\leq 1\%$ in the most recent calendar year, probably reflecting a learning curve and improved catheter technology. Arterial dissection and subsequent vessel closure has been identified as the most important factor related to PTCA complications in patients with predominantly normal ventricular function.¹⁶ The consequences of refractory arterial dissection and vessel closure were particularly high in our patients, and were the major cause of death. The 33% operative mortality from low-output syndromes in the 18 patients referred for urgent coronary artery bypass surgery is sobering, and higher than a previous series of patients treated urgently with predominantly normal ventricular function.¹⁷ Clearly, reductions in coronary flow, even for short periods of time, are tolerated poorly by patients with compromised ventricular function. Furthermore, attempts to reopen acutely occluded vessels with repeat PTCA could not prevent death in 9 patients with in-laboratory closure. In addition, 7 of the 12 patients dy-

FIGURE 1. Kaplan-Meier actuarial curves for total and event-free survival are displayed for patients with left ventricular dysfunction discharged from the hospital after percutaneous transluminal coronary angioplasty. The number of patients eligible at each interval and the total number of events are recorded.



ing after out-of-laboratory vessel closure did so despite immediate return to the catheterization suite for attempted redilatation. Prolonged inflations without interruption of anterograde flow are now possible with autoperfusion balloon catheters and may effectively stabilize >50% of severely dissected vessels.¹⁸ Furthermore, directional atherectomy and intravascular stents have proved useful for managing dissections refractory to prolonged inflations,^{19,20} and may enhance the procedural safety of PTCA in these patients in the near future.

An intraaortic balloon pump was used in only 113 procedures (13%), indicating that almost all patients with LV dysfunction can be successfully treated without support. Patients with the most severe ventricular dysfunction in association with critical anatomy, however, may benefit from supported PTCA. Our recent experience with elective placement of intraaortic balloon pumps before PTCA procedures, judged to be at extreme high risk for complications, suggests that this method is effective.²¹ An alternative PTCA support method receiving increasing attention is right atrial-femoral cardiopulmonary bypass placed either percutaneously or surgically.²² A large multicenter study of 105 patients treated with PTCA with cardiopulmonary bypass support included 35 patients with an ejection fraction <25% (23). Eight patients (8%) died during hospitalization. Vascular complications in both series were frequent due to the 18Fr to 20Fr cannulas required,^{22,23} but appear to be decreasing.²² Cardiopulmonary bypass support may provide greater circulatory support than intraaortic balloon counterpulsation in the setting of acute vessel closure and cardiac arrest, permitting more exhaustive attempts to reestablish coronary flow.

In our most recent 100 patients with moderate to severe LV dysfunction treated with PTCA, the predicted surgical operative mortality using the Coronary Artery Surgery Study formula was considerably higher (10.3%) than the observed mortal risk with PTCA (3%). Furthermore, the predicted surgical risk in these patients may underestimate their actual risk. Variables such as diffuse disease, distal disease, prior bypass surgery, and concomitant disabling medical problems were not factored into the prediction but were present in many of our patients.

Natural history studies of patients with coronary artery disease and LV dysfunction treated medically have demonstrated 4-year survival rates of approximately 35 to 60%.^{5,24-29} More favorable survival rates after coronary artery bypass surgery in patients with severe LV dysfunction (i.e., ejection fraction <35 to 40%) have been suggested by several nonrandomized series.^{5,25-29} The Coronary Artery Surgery Study nonrandomized

registry reported a cumulative survival of 72% at 4 years after bypass surgery in 231 patients with an ejection fraction $\leq 35\%$ compared with 61% in 420 patients treated medically.⁵ Hochberg et al⁶ observed a 3-year survival rate of 60% in 425 surgically treated patients with an ejection fraction between 20 and 39%, and only a 15% 3-year survival in 41 patients with an ejection fraction $\leq 20\%$.⁶ The 1- and 4-year actuarial survival rates of 87 and 69% respectively, after hospital discharge are similar to those reported by Kohli,⁹ Serota¹⁰ and their co-workers. Although survival after PTCA appears to be similar to that after bypass surgery, with a 15% crossover rate to coronary surgery, final conclusions must await the results of randomized trials.

This study has several important limitations. It is a nonrandomized series representing the results of a single group of experienced interventional cardiologists. Most patients in this study had a calculated ejection fraction from contrast ventriculography, whereas the others were entered into the study cohort on the basis of visually estimated ventricular function corroborated by a detailed clinical review. The similarities in the 2 groups suggests no selection bias, however. Criteria for patient selection for PTCA and balloon pump support were not established by protocol. However, the results do represent experiences with a broad spectrum of patients not limited by multiple exclusion criteria.

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Comparison of Exercise Radionuclide Angiography with Thallium SPECT Imaging for Detection of Significant Narrowing of the Left Circumflex Coronary Artery

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Although quantitation of exercise thallium tomograms has enhanced the noninvasive diagnosis and localization of coronary artery disease, the detection of stenosis of the left circumflex coronary artery remains suboptimal. Because posterolateral regional wall motion during exercise is well assessed by radionuclide angiography, this study determined whether regional dysfunction of the posterolateral wall during exercise radionuclide angiography is more sensitive in identifying left circumflex disease than thallium perfusion abnormalities assessed by single-photon emission computed tomography (SPECT). One hundred ten consecutive patients with CAD were studied, of whom 70 had a significant stenosis of the left circumflex coronary artery or a major obtuse marginal branch. Both regional function and segmental thallium activity of the posterolateral wall were assessed using visual and quantitative analysis. Left ventricular regional function was assessed objectively by dividing the left ventricular region of interest into 20 sectors; the 8 sectors corresponding to the posterolateral free wall were used to assess function in the left circumflex artery distribution. Similarly, using circumferential profile analysis of short-axis thallium tomograms, left ventricular myocardial activity was subdivided into 64 sectors; the 16 sectors corresponding to the posterolateral region were used to assess thallium perfusion abnormalities in the left circumflex artery territory.

Qualitative posterolateral wall motion analysis detected 76% of patients with left circumflex coronary artery stenosis, with a specificity of 83%, compared with only 44% by qualitative

thallium tomography ($p < 0.001$) and a specificity of 92%. Whereas quantitation of thallium activity increased the sensitivity for detecting left circumflex coronary artery stenosis to 80% with a specificity of 55%, it did not achieve statistical significance when compared with qualitative wall motion analysis. Similarly, quantitation of the posterolateral regional function did not improve the sensitivity for detecting left circumflex coronary artery stenosis (74%) when compared with qualitative regional function.

A similar analysis applied to the interventricular septum revealed a higher predictive accuracy for detecting left anterior descending coronary artery stenosis by qualitative thallium SPECT, with a sensitivity of 80% and a specificity of 71%, compared with a sensitivity of 68% and a specificity of 57% by qualitative radionuclide angiography. Quantitation of thallium activity in both septal and anterior regions provided no additional insight for detection of left anterior descending artery stenosis.

Thus, for noninvasive detection of left circumflex coronary artery disease, the data suggest that qualitative exercise radionuclide angiography is preferable to qualitative thallium SPECT and provides comparable information to quantitative thallium analysis.

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Stress thallium tomography has proved useful in identifying significant stenosis in individual coronary arteries¹⁻⁷ and thereby facilitating the evaluation and outcome of therapeutic interventions. Although the overall sensitivity of single-photon emission computed tomography (SPECT) for detection of coronary artery disease (CAD) is similar to that reported for quantitative planar imaging,^{4,8,9} SPECT has enhanced the localization of individual diseased coronary arteries when compared with planar thallium scintigra-

phy.^{1,2,5} However, for detecting significant left circumflex coronary artery stenosis, previous studies with thallium SPECT have reported a visual sensitivity in the range of only 42 to 63% and a quantitative sensitivity of 63 to 74% in patients without prior myocardial infarction.^{3-5,7} Because exercise radionuclide angiography in the left anterior oblique projection provides excellent visualization of the posterolateral wall motion, we hypothesized that evaluation of posterolateral regional function might identify disease in the left circumflex vascular territory with a greater sensitivity than thallium SPECT imaging. We therefore performed exercise thallium SPECT and exercise radionuclide angiography in a series of patients with CAD involving the left circumflex coronary artery.

METHODS

Patient selection: We studied 70 patients with CAD who had a significant stenosis in the left circumflex coronary artery or a major obtuse marginal branch. They represent a consecutive series of patients who were part of a larger series of 110 patients with CAD undergoing history and physical examination, chest x-ray, electrocardiography, coronary arteriography, exercise radionuclide angiography and thallium scintigraphy. Patients with a history of prior bypass surgery in the left circumflex coronary artery territory were excluded from the study in order to avoid the possibility of preserved flow in an area of prior lateral and posterior myocardial infarction. CAD was defined as $\geq 50\%$ reduction in luminal diameter of at least 1 major epicardial coronary artery as determined by coronary angiography. All cardiac medications were withdrawn before exercise studies in 56% of patients. In the other 44% of patients, the severity of anginal symptoms precluded discontinuation of medical therapy. We studied only patients with chronic stable CAD; no patient with recent acute myocardial infarction or unstable angina was included in the study. Ten patients had electrocardiographic evidence of prior myocardial infarction in the lateral and posterior leads (Q wave in leads I, AVL and V_5 - V_6 or tall R wave in leads V_1 - V_2 , or both). Ten patients had undergone previous coronary artery bypass surgery. The patients (67 men and 3 women) ranged in age from 33 to 79 years (mean 58).

Gated blood pool cardiac scintigraphy: Radionuclide angiography was performed at rest and during maximal supine bicycle exercise using red blood cells labeled in vivo with 20 to 25 mCi of technetium-99m. Imaging was accomplished using a conventional Anger camera equipped with a high-sensitivity parallel hole collimator oriented in a modified left anterior oblique position, as previously described.¹⁰ LV ejection fraction was derived by computer analysis of the time-activity

curves. The lower limit of normal for resting ejection fraction by our technique is 45% with a reproducibility limit of $\pm 4\%$.¹¹

Exercise studies were performed with use of a bicycle ergometer; exercise loads were increased by 25 W every 2 minutes until the development of angina, limiting dyspnea or fatigue. Patients who developed angina continued exercise until angina reached at least the severity that typically caused the patient to stop exercise. Data acquired only in the final 2 to 3 minutes of maximal exercise were selected for analysis.

QUALITATIVE REGIONAL ANALYSIS: Qualitative regional analysis was performed by 2 experienced investigators who were unaware of the results of coronary angiography or thallium scintigraphy. Regional wall motion analysis was confined to the left anterior oblique view, where the left ventricle was divided into septal, apical, lateral and basal regions. The function of each region was classified visually to be either normal or abnormal. Deterioration in regional function from rest to exercise was considered to be related to ischemia. Because the blood supply to the apical region is variable, this analysis was confined to the posterolateral wall supplied by the left circumflex coronary artery and the septal region supplied by the left anterior descending coronary artery. The right coronary artery territory was not studied because the exercise analysis was limited to the modified left anterior oblique projection, which prevents adequate assessment of inferior wall motion.

QUANTITATIVE REGIONAL ANALYSIS: Sector analysis for assessing regional ejection fraction was performed by subdividing the left ventricular region of interest into 20 angular sectors, each emanating from the diastolic left ventricular center of gravity, as previously described and validated in our laboratory.¹²⁻¹⁵ To facilitate comparison of these data with the qualitative interpretation, the sectors were then grouped and averaged into 4 myocardial regions. The 8 sectors corresponding to the posterolateral free wall (sectors 1 to 4, high lateral, and 17 to 20, low lateral) were used to assess function in the left circumflex artery territory (Figure 1). Similarly, the 8 sectors corresponding to the septal wall (sectors 7 to 10, high septal and 11 to 14, low septal) were used to assess function in the left anterior descending artery territory.

To obtain a normal data base for analysis of these regional data, we also studied 46 age comparable normal volunteers (mean age 54 years), who had no evidence of cardiovascular or pulmonary disease and whose physical examination, electrocardiogram and echocardiogram were normal. The posterolateral or the septal region in any patient with CAD was considered ischemic if the decrease in regional exercise ejection fraction was >2 standard deviations below the mean

change observed in the same region in normal subjects.¹³

Exercise thallium single-photon emission computed tomography imaging: After an overnight fast, exercise thallium scintigraphy was performed according to a standardized multistage treadmill exercise test protocol with continuous monitoring of symptoms, electrocardiogram, heart rate and blood pressure. Fifty percent of the patients achieved >85% of predicted heart rate during exercise. At peak exercise, 2 mCi of thallium-201 was administered intravenously and the patient continued exercise for an additional 45 to 60 seconds. After termination of exercise, thallium images were obtained using a wide field-of-view rotating gamma camera equipped with a low-energy, medium-resolution, high-sensitivity, parallel-hole collimator (Apex 415, APC-3, Elscint Company, Boston) centered on the 68-KeV photo peak with a 20% window. The camera was rotated over 180° in an elliptical orbit about the patient's thorax from a 40° right anterior oblique to a 40° left posterior oblique position at 6-degree increments for 30 seconds each. From the raw scintigraphic data, short-axis, vertical long-axis and horizontal long-axis tomograms were reconstructed as previously described,^{16,17} and 4 consecutive representative slices of each view were selected for interpretation. The reconstructed stress images were then analyzed both qualitatively and quantitatively.

QUALITATIVE THALLIUM ANALYSIS: The distribution of thallium activity was analyzed qualitatively in the short-axis and vertical long-axis tomographic views (4 slices per view). The stress images for each of the 110 patients were graded by 2 experienced observers on a 5-point scale, from 0 = markedly reduced/absent activity to 2 = definitely reduced and 4 = normal. The grade assigned to a region was the lowest regional score from all tomographic slices and views.

QUANTITATIVE THALLIUM ANALYSIS: The thallium images were also analyzed using a semiautomatic quantitative circumferential profile analysis applied to the short-axis thallium tomograms as previously described.^{16,17} Briefly, for each patient, an operator-defined region of interest was drawn around the left ventricular activity of each short-axis slice on the stress images. Myocardial activity was subdivided into 64 sectors, each emanating from the center of the tomograms. All 64 sectors were of equal arc and constructed beginning at 3 o'clock (midlateral wall) and proceeding counterclockwise. To facilitate comparison of these data with the qualitative interpretations, the sectors were then grouped and averaged into 4 myocardial regions. The 16 sectors corresponding to the posterolateral wall (sectors 1 to 8, high lateral; 57 to 64, low lateral) were used to assess thallium perfusion abnormalities in the left circumflex vascular territory. Similarly, the 16 sectors corresponding to the septal wall (sectors 24

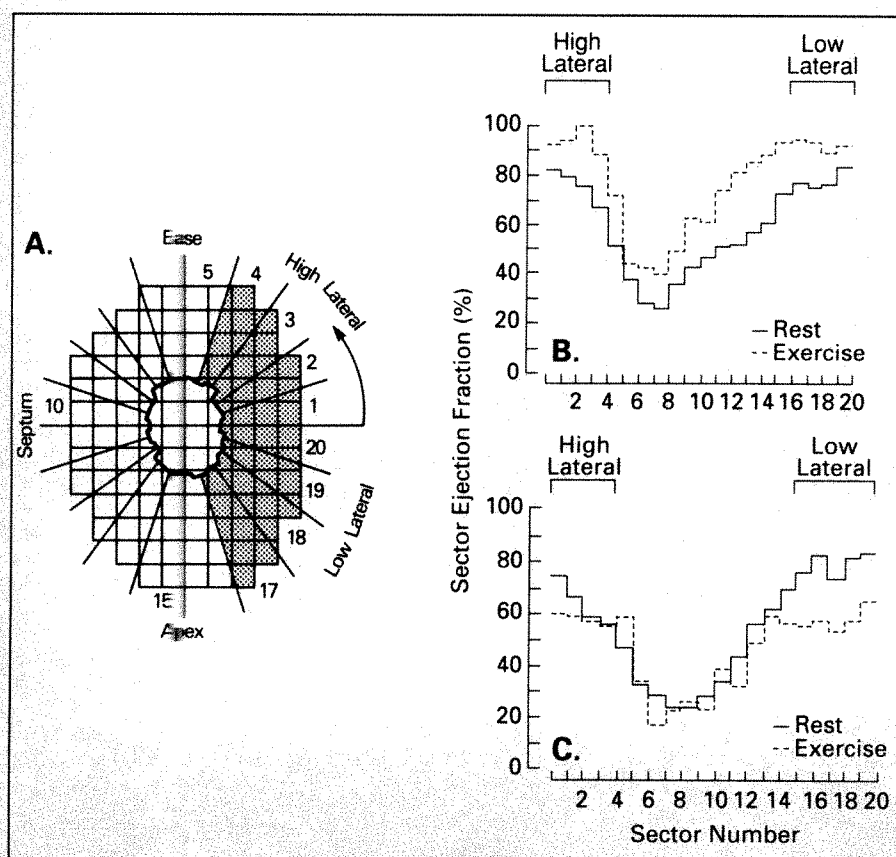


FIGURE 1. Regional left ventricular analysis was performed by subdividing the fixed left ventricular region of interest (panel A) into 20 angular sectors from which sector time-activity curves were constructed to compute the sector ejection fraction. For the purposes of this study, the 8 sectors corresponding to the posterolateral left ventricular free wall were analyzed. In this normal example (panel B), ejection fraction increases during exercise in all sectors. In contrast, in a patient with left circumflex coronary artery disease (panel C), ischemia is demonstrated in the posterolateral segment.

to 32, high septal; 32 to 40, low septal) were used to assess thallium perfusion abnormalities in the left anterior descending artery territory (Figure 2).

These data were then compared with a normal data base obtained from 50 normal volunteers (26 men and 24 women) who had no evidence of cardiovascular or pulmonary disease and whose physical examinations, electrocardiograms and echocardiograms were normal.¹⁶ The posterolateral and septal regions were considered abnormal in a patient with CAD if the thallium activity on the stress image was >2 standard deviations below the mean observed in the same region for the normal volunteers of the same sex.

Coronary arteriography: Cardiac catheterization was performed by the percutaneous femoral technique. Coronary artery stenosis and graft patency were assessed by an experienced cardiologist without knowledge of exercise thallium or radionuclide angiography results. Because the coronary vascular supply in the posterolateral region might be variable, the reviewer was specifically asked to identify the major vessel supplying the posterolateral free wall. As assessed by the reviewer's written interpretation of the coronary angiograms, the posterolateral wall was supplied by the left circumflex artery or obtuse marginal branches in all patients enrolled in the study. In 5 patients in whom the coronary angiograms were not available for review, this information was obtained from the official catheterization report available in their files. Of the 70 patients with left circumflex stenosis, 9 had significant narrowing of only the left circumflex artery or its branches, 17 had narrowing of 1 other coronary artery and 44 had 3-vessel CAD. In patients with bypass grafts, a vessel was considered patent if there was no significant narrowing within the graft or in the native coronary artery distal to the graft anastomosis.

Statistical analysis: Data are presented as mean \pm standard deviation. Regional ejection fraction data and relative regional thallium activity from normal volunteers were analyzed to derive normal confidence lim-

its. Differences between qualitative and quantitative assessment of segmental thallium activity and regional function were performed by chi-square analysis. Differences between exercise duration and rate-pressure product in patients with and without detectable thallium perfusion or regional wall motion abnormalities were performed by the unpaired *t* test. Differences between patients with and without thallium perfusion abnormalities achieving $>85\%$ predicted maximal heart rate were performed by chi-square analysis.

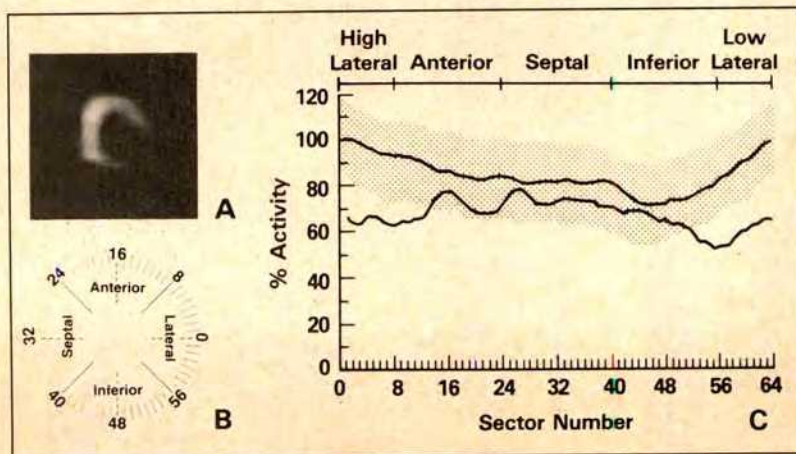
RESULTS

Detection of left circumflex coronary artery stenosis:

RADIONUCLIDE ANGIOGRAPHIC DATA: LV ejection fraction in the 70 patients ranged from 15 to 80% (mean 44 ± 15) at rest and from 9 to 75% (mean 39 ± 15) during exercise. Ejection fraction either decreased or did not change from the value at rest in 61 (87%) patients. By visual analysis, exercise-induced posterolateral wall motion abnormalities developed in 53 of the 70 patients (76%), of whom 17 (24%) also had posterolateral wall motion abnormalities at rest. The other 17 patients had normal posterolateral wall motion both at rest and during exercise. When the 2 patient groups with and without detectable posterolateral wall motion abnormalities by qualitative analysis were compared, the rate-pressure product achieved during exercise was higher in those with than without posterolateral wall motion abnormalities ($18.6 \pm 4.0 [10^3]$ vs $17.5 \pm 5.0 [10^3]$, $p < 0.01$) despite slightly shorter exercise duration (4.7 ± 1.7 vs 5.0 ± 2.0 minutes, $p < 0.01$).

The quantitative data regarding regional ejection fraction derived from sector analysis are displayed in Figure 3 for a patient with 1-vessel left circumflex CAD. Regional ejection fraction during exercise was abnormal in either the high or low lateral wall in 52 of the 70 patients (74%). When all 8 sectors representing the posterolateral free wall were assessed collectively, the mean regional ejection fraction during exercise was

FIGURE 2. Sector analysis for assessing regional myocardial thallium activity. A short-axis thallium-201 tomogram obtained after exercise is shown for a patient with coronary artery disease in panel A. The left ventricular myocardium is then subdivided into 64 sectors representing 4 myocardial regions (panel B). Thallium activity during stress in each sector is displayed (panel C) and compared with the normal range (mean ± 2 standard deviations observed for normal volunteers), represented as the shaded area with center line. For the purposes of this study, the 16 sectors corresponding to the posterolateral region were analyzed. In this example, thallium perfusion defects are apparent in the posterolateral region.



$63 \pm 18\%$ in the patients with CAD compared with $90 \pm 8\%$ in the normal volunteers. Quantitative analysis detected 5 of 8 (62%) patients with 1-vessel left circumflex coronary artery stenosis, and 47 of 62 (76%) patients with ≥ 2 -vessel disease. In 60 patients without Q waves involving the lateral leads, the sensitivity for detecting left circumflex CAD using exercise radionuclide angiography was 73% by qualitative and 73% by quantitative analyses. Similarly, exercise radionuclide angiography detected posterolateral wall motion abnormalities in 8 of 10 patients (80%) with prior myocardial infarction in the left circumflex artery territory, by both qualitative and quantitative analysis.

This quantitative method was also applied to the 53 regions identified to have posterolateral abnormal wall motion by qualitative analysis. Regional sector analysis confirmed 42 of 53 regions (79%) to be abnormal, with a mean regional ejection fraction of $61 \pm 18\%$ in all lateral sectors collectively. Furthermore, of the 17 regions that were considered normal by visual analysis,

quantitative regional analysis identified 10 (59%) to be abnormal, with a mean regional ejection fraction of $65 \pm 19\%$. Thus, 52 of 70 patients (74%) with significant left circumflex CAD demonstrated abnormal regional function by quantitative analysis (Figure 4).

THALLIUM TOMOGRAPHIC DATA: Among the 70 patients with significant stenosis in the left circumflex coronary artery, 31 (44%) developed visually apparent exercise-induced thallium perfusion defects in the posterolateral wall, whereas the remaining 39 patients had apparently normal thallium activity in this region. Of the 31 posterolateral regions identified to have abnormal thallium activity by qualitative analysis, 29 (94%) were confirmed to be abnormal by quantitative analysis. Furthermore, of the 39 regions that were perceived to be normal by qualitative analysis, thallium quantitation identified 27 (69%) to be abnormal. Thus, 56 of the 70 patients (80%) with significant left circumflex CAD demonstrated abnormal posterolateral thallium activity by quantitative analysis, and the remaining 14

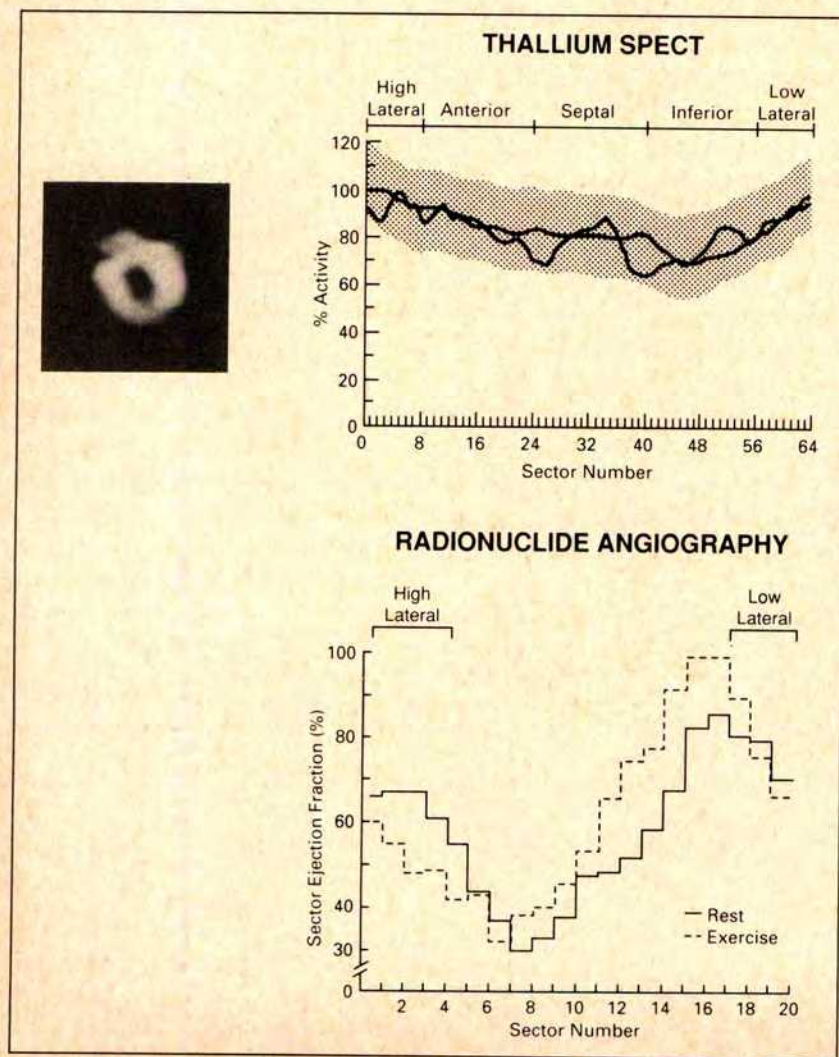


FIGURE 3. Circumferential profile analysis and regional ejection fraction plotted for a patient with 1-vessel left circumflex coronary artery disease. Both the short-axis thallium-201 tomogram and the quantitative thallium single-photon emission computed tomography (SPECT) profile obtained after exercise are normal (top), whereas ischemia is demonstrated in the lateral region by exercise radionuclide angiography (bottom).

had normal thallium activity (Figure 4). When the 2 patient groups, with and without detectable thallium perfusion abnormalities by quantitative analysis, were compared, the percentage of patients achieving $>85\%$ predicted maximal heart rate was the same (48 vs 53%, respectively, $p = \text{not significant}$), and the rate-pressure product was lower in those with than without posterolateral perfusion defects ($19.6 \pm 6.0 [10^3]$ vs $22.5 \pm 6.6 [10^3]$, $p < 0.01$). As such, quantitative thallium SPECT failed to identify 20% of patients with significant left circumflex stenosis, despite these higher rate-pressure products.

The quantitative data regarding regional thallium activity derived from circumferential profile analysis are displayed in Figure 2 for a patient with left circumflex CAD. In this patient, thallium activity in the myocardial sectors in the posterolateral region were abnormal during exercise (i.e., below the normal range). Thallium quantitation detected 7 of 9 patients (78%) with 1-vessel left circumflex artery stenosis, and 49 of 61 patients (80%) with ≥ 2 -vessel disease. In 60 patients without electrocardiographic evidence of Q waves in the lateral leads, the sensitivity for detecting left circumflex CAD using thallium SPECT was 40% by qualitative and 81% by quantitative analyses. Similarly, in 10 patients with electrocardiographic evidence for prior myocardial infarction in the lateral leads, quantitative thallium SPECT detected perfusion abnormalities in 8 patients (80%).

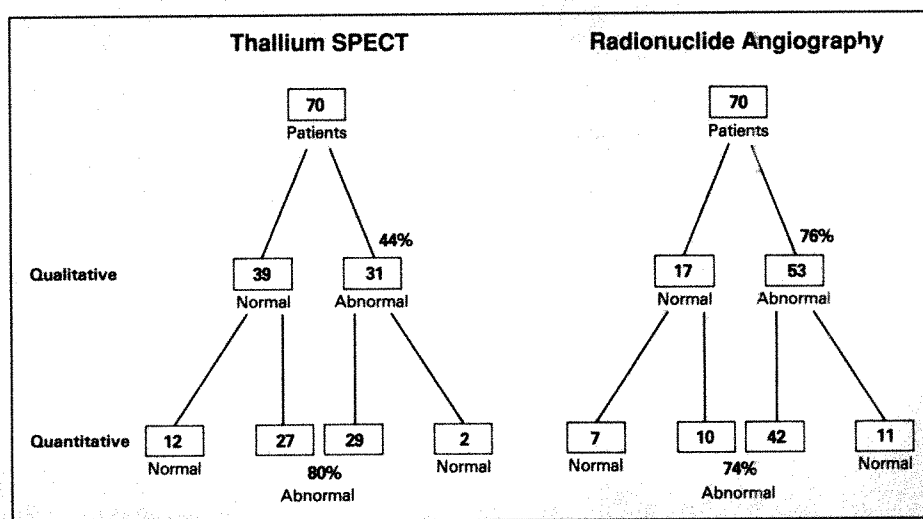
COMPARISON OF PERFUSION AND FUNCTIONAL DATA: There was concordance between qualitative thallium perfusion and posterolateral wall motion in 34 regions (49%). Of the remaining 36 discordant regions, 29 (81%) had normal thallium perfusion but abnormal wall motion and only 7 regions with normal wall motion had abnormal thallium activity. Similarly, there

was concordance between quantitative thallium activity and regional ejection fraction in 49 regions (70%). Of the remaining 21 discordant regions, 9 (43%) demonstrated normal thallium activity but abnormal regional ejection fraction, and 12 regions (57%) had normal regional function but reduced thallium activity. The results of detecting left circumflex stenosis by exercise radionuclide angiography or thallium SPECT did not differ between patients who were studied with and without antianginal medications.

When the exercise radionuclide angiographic and stress thallium scintigraphic data were analyzed in combination, 59 of the 70 patients (84%) had evidence of impaired function or perfusion in the left circumflex coronary artery territory using qualitative analysis, and 64 (91%) had evidence of left circumflex disease using quantitative analysis. The combined analysis of qualitative thallium perfusion and regional function did not significantly improve the sensitivity for detecting left circumflex coronary artery stenosis when compared with qualitative regional function alone (84 vs 76%, respectively). However, the combined analysis of quantitative data from both the thallium and radionuclide angiographic studies improved the diagnosis of left circumflex stenosis beyond the results of qualitative exercise radionuclide angiography alone (91 vs 76%, respectively, $p < 0.05$).

SPECIFICITY OF PERFUSION AND FUNCTIONAL DATA: Among the 40 patients with CAD in the absence of significant left circumflex stenosis, 37 (92%) had visually normal thallium activity in the posterolateral wall, whereas the remaining 3 had apparently abnormal thallium activity in this region. When quantitative analysis was performed, all 3 regions that were perceived to be abnormal by qualitative analysis were confirmed to be abnormal by quantitation. However, of the 37 re-

FIGURE 4. Flow diagrams displaying the frequency of left circumflex coronary artery detection using exercise thallium single-photon emission computed tomography (SPECT) versus exercise radionuclide angiography for qualitative and quantitative analyses.



gions that were identified to have normal thallium activity by qualitative analysis, thallium quantitation identified 15 (40%) to be abnormal. Thus, the specificity for detecting a significant left circumflex CAD using quantitative analysis was only 55%.

When posterolateral wall motion abnormalities were assessed by visual analysis, 8 of the 40 patients developed apparent exercise-induced hypokinesia and 32 (80%) had normal posterolateral wall motion both at rest and during exercise. Quantitative functional analysis confirmed all 8 regions to be abnormal. However, of the 32 regions that were identified to have normal thallium activity by qualitative analysis, quantitation identified 5 (16%) to be abnormal. Thus, the specificity for detecting a significant left circumflex CAD using quantitative functional analysis was 66%.

Detection of left anterior descending coronary artery stenosis: When qualitative septal regional wall motion abnormalities were assessed in the modified left anterior oblique view (providing best septal separation), the sensitivity for detecting left anterior descending artery stenosis was 68% and the specificity was 57%. Quantitative regional ejection fraction did not improve either the sensitivity (74%) or the specificity (50%) for detecting left anterior coronary artery stenosis when compared with visual analysis.

When qualitative regional thallium activity was assessed in the septal region alone, the sensitivity (69%) and the specificity (71%) for detecting significant left anterior descending coronary artery stenosis was similar to that obtained by exercise radionuclide angiography. However, when qualitative regional thallium activity was assessed in both septal and anterior myocardial regions (which can be assessed by thallium SPECT but not by exercise radionuclide angiography), the sensitivity for detecting significant left anterior descending coronary artery stenosis increased to 80%, with a specificity of 71%. Quantitation of thallium activity in both septal and anterior regions provided no additional insight for detecting left anterior descending coronary artery stenosis, with a sensitivity of 80% and a specificity of 60%.

DISCUSSION

The results of the present investigation, involving a consecutive series of patients with CAD, indicate that the sensitivity of qualitative thallium tomography for detecting left circumflex coronary artery stenosis is low (only 44%), but that this increased significantly to 80% by quantitative analysis of the thallium data ($p < 0.001$). These latter results are similar to the sensitivity reported by Maddahi et al⁶ using the bullseye program. However, qualitative posterolateral wall mo-

tion analysis of the radionuclide angiographic data detected 76% of patients with left circumflex coronary artery stenosis, significantly higher than qualitative thallium tomography ($p < 0.001$) and comparable to quantitative thallium analysis. Quantitative functional analysis applied to the posterolateral regions judged to be abnormal by qualitative analysis confirmed these regions to be abnormal.

Although an abnormal ejection fraction response with exercise or regional wall motion abnormality correlates with significant CAD¹⁸⁻²¹ and provides important prognostic information,²²⁻²⁴ its application for detecting individual coronary artery stenosis has been limited. In 1981, Elkayam et al,²⁰ comparing qualitative planar thallium images with exercise radionuclide angiograms, reported that visually apparent abnormalities of regional wall motion were more sensitive than thallium perfusion for detecting left anterior descending CAD (80 vs 55%) and left circumflex disease (58 vs 40%), although the latter did not achieve statistical significance. However, no data are available that compare quantitative stress thallium SPECT with quantitative exercise radionuclide angiography for detecting left circumflex coronary artery stenosis.

There are several factors that may explain the improved sensitivity of qualitative exercise radionuclide angiography over thallium tomography. As thallium activity in the posterolateral region is only slightly attenuated relative to the inferior and septal regions, the posterolateral wall has the highest thallium counts in tomographic images of the normal left ventricle. Thus, it is often difficult to detect subtle thallium perfusion abnormalities visually within the posterolateral region, because thallium activity may remain greater than or similar to thallium activity in other vascular territories. This would especially be the case in patients with multivessel disease, in whom equivalent reduction in perfusion in several regions would still result in greater thallium activity in the posterolateral territory. Although quantitation of thallium tomograms improves the sensitivity of detecting left circumflex CAD, since the mean counts per pixel at peak exercise within the posterolateral region is compared with the normal data base independent of other regions, the sensitivity derived from quantitative programs remains suboptimal. This may be explained by the normalization processes. Objective analysis of thallium tomograms relies on normalized data, in which the region with greatest thallium activity is set to 100% and other regions are analyzed relative to this reference standard. As thallium activity is usually highest in the posterolateral wall, in most circumstances the regional tomographic data are normalized to the thallium activity in the posterolateral wall, which then

becomes the "normal" reference standard. Thus, the same factors that limit the sensitivity for detecting left circumflex disease using visual analysis may also reduce the sensitivity of objective programs as well. In contrast, wall motion of the posterolateral region is well visualized by radionuclide angiography performed in the best septal left anterior oblique view. Quantitative assessment of regional posterolateral function using sector analysis confirms and may further improve the identification of focal and mild posterolateral wall motion abnormalities not readily appreciated by visual analysis.

In clinical practice, exercise cardiac studies using a radionuclide tracer are usually performed for 1 of 2 purposes. The first is to determine whether a significant coronary artery stenosis is present. The second is to determine the extent of the myocardial territory supplied by a coronary artery with a proved stenosis and the prognostic implications thereof. Determining which coronary artery is stenosed is usually not an issue on the initial evaluation of patients being screened for presence of CAD. Thus, for the initial detection of CAD, both exercise thallium SPECT and exercise radionuclide angiography provide comparable information. The issue of which individual coronary artery is involved becomes relevant when the physiologic significance of a specific coronary artery stenosis is in question in a patient who has already undergone coronary arteriography. This is a very common clinical situation. This determination is quite important, for subsequent clinical decisions regarding revascularization may depend on the results of the specific noninvasive test performed. In these clinical situations, if the coronary artery stenosis in question is the left circumflex coronary artery, our results suggest that for nuclear cardiology laboratories interpreting thallium images using purely qualitative approaches, qualitative exercise radionuclide angiography is preferable to qualitative thallium SPECT and is comparable to quantitative thallium SPECT. However, because the acquisition of exercise radionuclide data in the modified left anterior oblique view precludes regional assessment for right coronary artery stenosis, and limits the assessment of the left anterior descending coronary artery solely to the septum, we do not advocate using exercise radionuclide angiography instead of thallium tomography for detecting right and left anterior descending coronary artery stenoses.

Although the specificity of quantitative thallium SPECT for detecting left circumflex stenosis may appear to be low in our study (55%) compared with the 91% reported by Mahmarian et al,²⁵ it is similar to the 60% specificity reported by Maddahi et al.⁶ Specificities for detecting individual coronary artery stenoses

may vary among institutions and is dependent on the patient population studied, quantitation program used, and the standard deviation chosen from the mean in normal volunteers.

It is well documented that other disease processes, such as valvular heart disease or cardiomyopathies, may cause abnormal LV function with exercise, both regionally and globally. Since the patients in the current study represent those with pure CAD, the results may not pertain to detecting ischemia in the left circumflex territory in patients known or suspected to have other associated diseases. In such situations, exercise thallium SPECT is superior diagnostically to exercise radionuclide angiography.

Thus, in patients without concomitant noncoronary disease, our results suggest that exercise radionuclide angiography may be used instead of thallium tomography for the serial evaluation of patients with significant left circumflex CAD. This can be accomplished using qualitative analysis and does not require a quantitative method. Because many (if not most) nuclear cardiology laboratories interpret thallium images using purely qualitative approaches, these data indicate that exercise radionuclide angiography may be preferable to qualitative thallium tomography for the noninvasive evaluation of left circumflex coronary artery stenosis. However, when thallium images are interpreted using quantitation programs, both techniques are quite comparable for identifying left circumflex coronary artery stenosis.

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Stunned Left Ventricular Myocardium After Exercise Treadmill Testing in Coronary Artery Disease

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Myocardial stunning (postischemic ventricular dysfunction) occurs in dogs after coronary stenosis following treadmill exercise. Less data are available in humans regarding development of stunned myocardium after exercise. Regional wall motion changes were evaluated in 22 patients with known coronary artery disease using 2-dimensional echocardiography and exercise treadmill testing. Wall motion was scored as 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic. At least 1 left ventricular segment with normal resting function developed an increase in wall motion score at 15 or 30 minutes compared with values at rest. The wall motion score in the midportion of the ventricular septum increased from 1.0 at rest to 1.6 ($p < 0.004$) at 30 minutes after exercise; the basal inferior wall score worsened from 1.0 at rest to 1.9 ($p < 0.01$) at 30 minutes after exercise. Coronary angiographic data in these patients revealed that left anterior descending narrowing correlated best with left ventricular septal wall motion abnormalities, whereas right coronary artery and circumflex narrowing best correlated with inferior and posterior wall motion abnormalities. Eight normal adult volunteers with no history of myocardial ischemia also underwent 2-dimensional echocardiography and exercise testing. No wall motion abnormalities were observed at any time after exercise. The present study suggests that in patients with coronary artery disease, exercise treadmill testing may induce regional wall motion abnormalities of the left ventricle that persist ≥ 30 minutes after exercise, an observation consistent with the phenomenon of stunned myocardium.

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Myocardial stunning refers to postischemic ventricular dysfunction.^{1,2} This phenomenon has been observed in experimental animal models of brief complete coronary artery occlusion followed by reperfusion.³ There is now evidence that a similar phenomenon occurs in animals⁴ when myocardial ischemia is induced by increasing demand in the setting of a partial coronary stenosis. Little information is available on whether this same phenomenon occurs in patients who undergo exercise stress testing.

Robertson et al⁵ used 2-dimensional echocardiography to examine wall motion abnormalities during and 30 minutes after exercise testing. In 4 of 8 patients with significant 2-vessel coronary artery narrowing and in 2 of 2 patients with 3-vessel coronary narrowing, persistent regional wall motion abnormalities were observed at 30 minutes. Our study seeks to determine whether persistent wall motion abnormalities occur in a group of patients with known coronary artery disease after exercise treadmill testing and to semiquantitate and further characterize this phenomenon.

METHODS

We studied 22 patients who were referred for exercise treadmill testing as a part of evaluation for either known or suspected coronary artery disease. All 22 patients studied had angiograms recorded either before or after the exercise test, confirming the presence of coronary artery disease. Patients performed either a standard or modified low level Bruce protocol exercise test. Two-dimensional echocardiograms were obtained before, immediately after, and 15 or 30 minutes, or both, after exercise, to assess regional wall motion abnormalities.

Four views of the heart (parasternal long and short axis, and apical 4- and 2-chamber views) were attempted at each time point. Regional wall motion abnormalities of the left ventricle were graded by 2 observers (by consensus) at each time point. The 16 walls of the left ventricle that were graded are shown in Figure 1. A semiquantitative scoring system was used to grade regional wall motion as has been described previously⁶: (grade 1 = normal contraction, grade 2 = hypokinesia, grade 3 = akinesia, and grade 4 = dyskinesia). Grades

2 to 4 were associated with either reduced or absent wall thickening during systole; grade 4 was often associated with paradoxical wall thinning. If a wall was not well visualized during the study it was not scored. All patients developed wall motion abnormality(ies) during ≥ 2 of the time periods, confirming that coronary artery disease was associated with physiologic abnormality.

Agreement by the readers on multiple readings of the same echocardiograms read months apart was good. In a series of 12 patients, mean wall motion score was 1.34 on the first and 1.36 on a later reading.

Analysis of 2-dimensional echocardiogram was performed using an ACUSON 128 channel system interfaced to a GTI Freeland cineviewer. Direct acquisition recording was used to reduce image degradation. Images were acquired with an audio trigger interfaced to the electrocardiogram. The images were displayed in a quad-screer format of parasternal long and short axis, and apical \leftarrow and 2-chamber views. Continuous systolic loops were displayed.

The end points of the study were to determine whether left ventricular wall segments that were normal at rest showed wall motion abnormalities at 15 or 30 minutes, or both, after exercise compared with the resting values.

Eight normal adults with no history of coronary artery disease (angina, myocardial infarction) also were studied in this manner as controls. The Wilcoxon rank test was used to compare 2-dimensional echocardiographic scores immediately after, and at 15 and 30 minutes after exercise versus rest.

RESULTS

Patient group: Patient age in the coronary artery disease group (19 men and 3 women) ranged from 44 to 86 years (mean 63). Seventeen of the 22 patients had a history of angina pectoris; 15 had a previous myocardial infarction that healed. Four of the 22 patients were receiving β blockades, 5 were receiving long-acting nitrates and 6 were receiving calcium an-

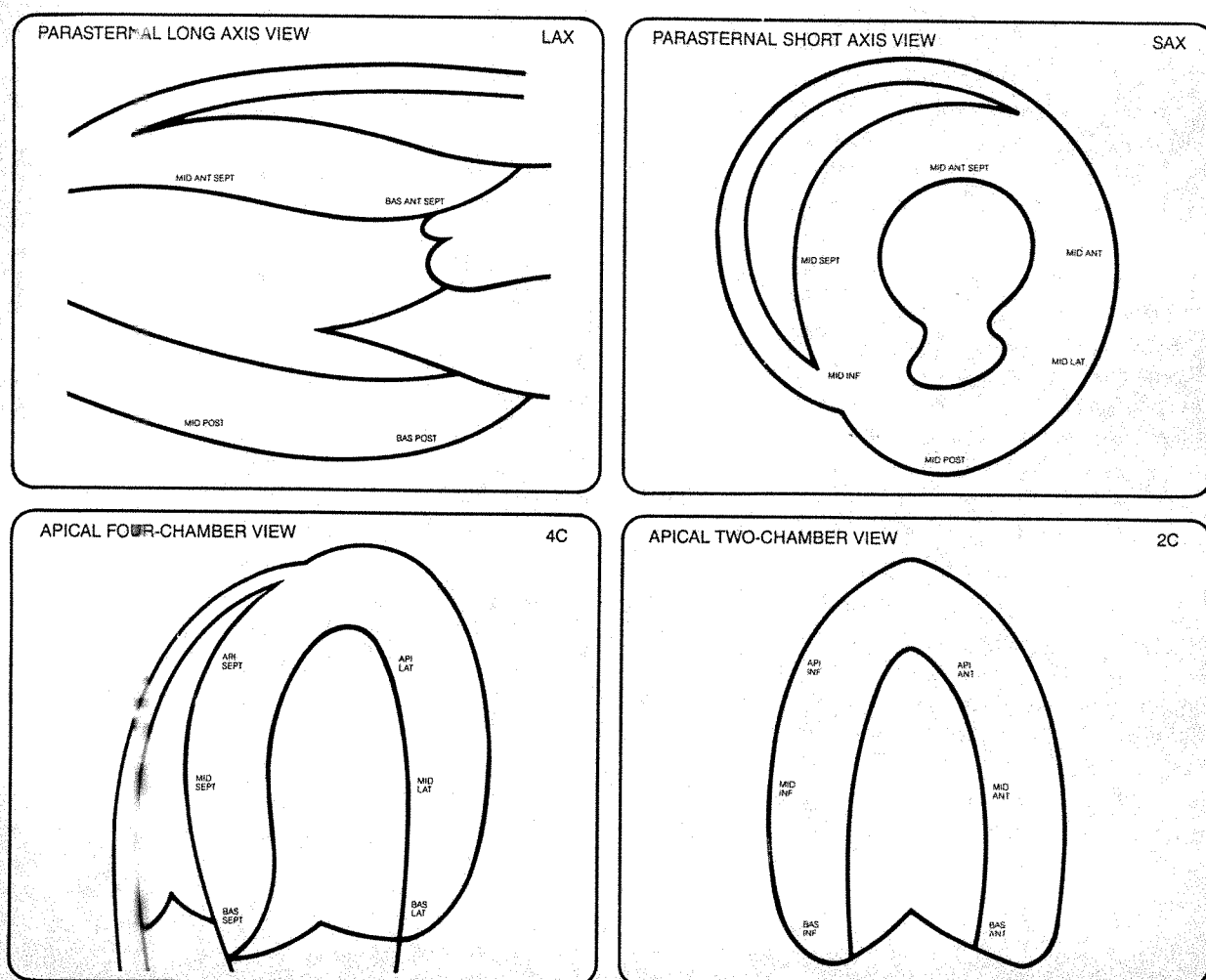


FIGURE 1. Representation of the 4 echocardiographic views obtained. ANT = anterior; API = apical; BAS = basal; C = chamber; INF = inferior; LAT = lateral; LAX = long axis; POST = posterior; SAX = short axis; SEPT = septum. Diagrams courtesy of G.T.I. Freeland.

TABLE I Patient Demographic, Angiographic and Two-Dimensional Echo-Exercise Data

Pt.	Age (yr) & Sex	Angina	Old MI	Previous PTCA, CABG	Angiographic Data*				New Wall Motion Abnormality†		
					R	LM	LAD	LC	Immediately After Exercise	15 Minutes After Exercise	30 Minutes After Exercise
1	74M	+	-	+	90	0	90	90	+	+	+
2	54M	-	+	+	40	0	98	100	-	+	+
3	74M	-	-	+	0	0	99	0	+	+	+
4	58M	+	+	-	100	0	85	75	+	NA	+
5	64M	-	-	+	95	0	0	0	-	+	+
6	44M	+	+	-	25	0	50	25	+	+	+
7	67M	+	+	+	100	70	60	90	+	+	+
8	63M	+	-	-	0	0	90	75	+	+	NA
9	71M	+	+	-	45	0	95	99	+	+	+
10	52F	+	+	+	100	0	100	0	-	+	+
11	54M	+	+	+	100	90	90	0	+	NA	+
12	66M	+	+	+	100	0	100	100	+	+	+
13	86M	-	-	-	80	0	25	0	+	+	+
14	72M	+	+	-	100	50	100	90	+	NA	+
15	68F	+	+	+	30	0	90	90	-	+	+
16	58M	+	+	+	95	0	75	30	+	-	+
17	62M	-	+	+	99	80	99	50	+	+	+
18	78F	+	-	-	80	0	95	100	+	+	-
19	45M	+	+	+	95	0	75	95	-	+	+
20	52M	+	+	-	90	0	90	90	+	+	-
21	71M	+	+	+	99	0	99	99	-	+	+
22	61M	+	-	-	0	0	60	0	+	+	+

*Numbers represent maximal stenosis on angiography.

†Last 3 columns show whether patient had an increase in wall motion score: + = present; - = absent compared with 1 (normal) value at rest in at least 1 wall of the left ventricle. Wall motion abnormality was determined by echocardiography.

CABG = coronary artery bypass grafting; LAD = left anterior descending artery; LC = left circumflex artery; LM = left main coronary artery; MI = myocardial infarction; NA = not available; PTCA = percutaneous transluminal coronary angioplasty; R = right coronary artery.

tagonists. Thirteen patients had previous coronary angioplasty ($n = 3$) or coronary bypass surgery ($n = 10$); 3 patients had these procedures after the exercise test. ST-segment depression diagnostic of ischemia occurred in 10 of 22 patients during exercise. Eight patients stopped exercising because of chest pain, 8 stopped because of dyspnea, and 16 patients complained of leg fatigue. All patients exercised to a symptom limited end point. At peak exercise, mean heart rate \pm standard deviation was 128 ± 23 beats/min, and mean systolic and diastolic blood pressures were 167 ± 32 and 78 ± 12 mm Hg, respectively.

Patient age in the normal volunteer group (all men) ranged from 41 to 65 years. No patient developed chest pain. Patients stopped because of fatigue. At peak exercise, mean heart rate was 174 ± 23 beats/min, and mean systolic and diastolic blood pressures were 188 ± 16 and 87 ± 4 mm Hg, respectively.

Echocardiographic results in patients with coronary artery disease: Three patients did not have 15-minute but did have 30-minute postexercise recordings. One patient had a 15-minute but not a 30-minute postexercise reading. All other patients had both 15- and 30-minute postexercise recordings.

Between rest and immediately after exercise, 16 of 22 patients (73%) who had left ventricular segments with normal resting function developed wall motion abnormalities of at least 1 wall (Table I). Three of the 16

walls of the left ventricle showed significant increases in score from normal rest values to immediately after exercise. The midinferior wall increased its score from 1.0 to 1.4 ($p < 0.02$), the midportion of the ventricular septum from 1.0 to 1.4 ($p < 0.02$), and the basal inferior wall from 1.0 to 2.0 ($p < 0.01$).

Eighteen of 19 patients (95%) who had left ventricular segments with normal function at rest and echocardiograms available at 15 minutes developed an increase in wall motion score at 15 minutes compared with rest values in at least 1 wall (Table I). Wall motion score deteriorated significantly between rest and 15 minutes in 5 of 16 of these walls. The midanterior septum increased from a score of 1.0 at rest to 1.5 at 15 minutes ($p < 0.01$), as did the midportion of the ventricular septum (from 1.0 to 1.6, $p < 0.01$), midanterior wall (from 1.0 to 1.3, $p < 0.04$), basal inferior wall (from 1.0 to 2.0, $p < 0.03$) and midportion of the inferior wall (from 1.0 to 1.6, $p < 0.01$).

Nineteen of 21 patients (90%) who had left ventricular segments with normal function at rest and echocardiograms available at 30 minutes developed an increase in wall motion score at 30 minutes in at least 1 wall compared with rest values (Table I, Figure 2). Significant increases in these scores occurred in 6 of 16 walls at 30 minutes. The midanterior septum increased its score at 30 minutes compared with rest values (from 1.0 to 1.6, $p < 0.002$), as did the midinferior

wall (from 1.0 to 1.7, $p < 0.001$), midportion of the septum (from 1.0 to 1.6, $p < 0.004$), apical septum (from 1.0 to 1.5, $p < 0.03$), apical-lateral (from 1.0 to 1.4, $p < 0.03$), and basal-inferior walls (from 1.0 to 1.9, $p < 0.01$).

Left ventricular segments that were abnormal at rest (score of ≥ 2) generally remained the same or worsened slightly at 15 to 30 minutes after exercise.

Echocardiographic data in normal volunteers: All 8 patients in the normal volunteer group demonstrated normal left ventricular wall motion at rest, immediately after exercise, and at 15 and 30 minutes after exercise. Thus, no wall motion abnormalities were observed at any time in these patients.

Coronary angiographic data: Coronary angiographic data in the patients referred for coronary artery disease are listed in Table I. Narrowing $\geq 50\%$ was observed in a single epicardial coronary artery (either right, left main, left anterior descending or circumflex) in 5 patients, in 2 vessels in 6 patients, and ≥ 3 vessels in 11 patients.

Seventeen of 20 patients (85%) with left anterior descending disease had a wall motion abnormality in the ventricular septal wall at 30 minutes. Nineteen of

20 patients (95%) with left anterior descending disease had a wall motion abnormality in the septum at either 15 or 30 minutes. Eighteen of 20 patients with left anterior descending disease (90%) had an increase in septal wall motion score at 15 or 30 minutes compared with rest values.

Wall motion abnormalities in other ventricular walls besides the septum did not correlate as well with left anterior descending disease. For example, only 13 of 20 patients (65%) with left anterior descending disease had a wall motion abnormality present in the anterior wall at 15 or 30 minutes, and 9 of 20 (45%) had an increase in anterior wall motion score at 15 or 30 minutes. Sixteen of 20 patients (80%) with left anterior descending disease had a wall motion abnormality in the apex at 15 or 30 minutes. Ten of 20 (50%) had an increase in apical wall score at 15 or 30 minutes compared with rest scores.

Conversely, only 2 of 22 patients (9%) with septal wall motion abnormality had no left anterior descending disease, 0 of 16 patients with anterior wall motion abnormalities had no left anterior descending disease, and 1 of 17 patients (6%) with apical wall motion abnormality had no left anterior descending disease.

Disease in the right coronary and circumflex arteries correlated best with wall motion abnormalities in the inferior or posterior LV walls, or both. For example, 15 of 15 patients (100%) with right coronary artery disease had a wall motion abnormality in the inferior or posterior left ventricular walls at 15 or 30 minutes after exercise. Fourteen of 15 (93%) with right coronary artery disease had worsened wall motion in the inferior or posterior walls, or both, at 15 or 30 minutes compared with rest scores. Similarly, 14 of 14 patients (100%) with circumflex artery disease had a wall motion abnormality at 15 or 30 minutes in the inferior or posterior walls, or both. Thirteen of 14 patients (93%) with circumflex disease had worsening of inferior or posterior wall function at 15 or 30 minutes compared with rest scores. Ten of 14 patients (71%) with circumflex disease had a lateral wall motion abnormality at 15 or 30 minutes, and only 2 of these patients had worsened left ventricular function in the lateral wall at 15 or 30 minutes.

Conversely, only 3 of 20 patients (15%) with inferior or posterior wall motion abnormalities, or both, did not have disease of the right coronary or circumflex artery. Four of 14 patients (29%) with lateral wall motion abnormalities did not have disease of the circumflex artery.

DISCUSSION

Exercise stress testing in patients with coronary artery disease was associated with regional wall motion

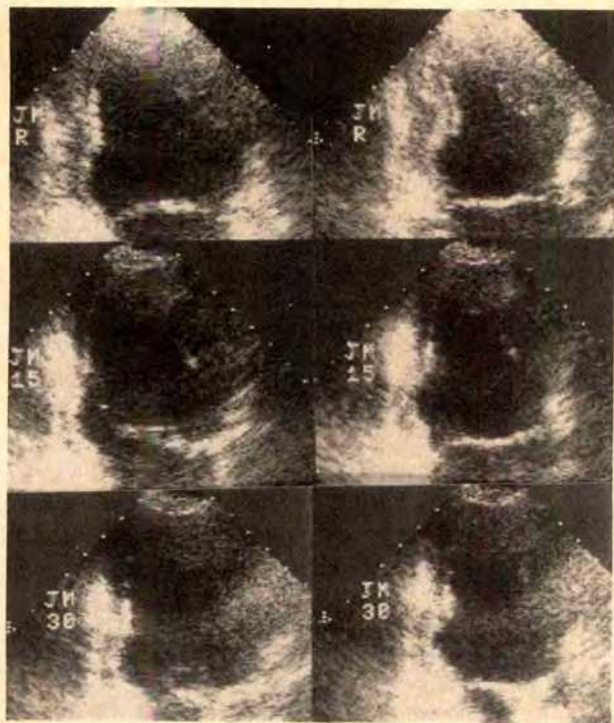


FIGURE 2. Apical 2-chamber views of a patient with 3-vessel coronary artery disease at rest (top row), and 15 (middle row) and 30 (bottom row) minutes after exercise. Photographs at left represent end diastole and at right end systole. The inferoapical and anterior walls thicken normally at rest with a reduction in left ventricular diameter. Thirty minutes after exercise there is less thickening toward the apical half of the ventricle and the left ventricular diameter appears wider than at rest (compare lower right with upper right figures).

abnormalities at 15 and 30 minutes after exercise, at a time when chest pain and electrocardiographic abnormalities are usually resolved. These findings may represent a form of stunned myocardium and may be analogous to the experimental work of Homans et al⁴ in which dogs with partial stenoses, placed on a treadmill, developed prolonged wall motion abnormalities after exercise. Ischemia induced by a partially stenosed coronary vessel and exercise may be sufficient to induce stunned myocardium; a total coronary artery occlusion may not be needed.

Two-dimensional echocardiography is an important technique for evaluating and diagnosing coronary artery disease.⁵ Regional ventricular wall motion abnormalities on 2-dimensional echocardiography are readily visible, and the technique used in association with exercise testing allows detection of ischemic myocardium. Two-dimensional echocardiography allows visualization of the entire thickness of the left ventricular wall and thus allows wall thickening to be examined. However, radionuclide ventriculographic studies only examine a blood pool image. Thus, only the movement of the endocardium is visualized and extent of wall thickening cannot be appreciated by this nuclear technique. This fact helps to explain why, in a previous study using radionuclear ventriculography, prolonged wall motion abnormalities were not observed after termination of exercise.⁷ Positron emission tomographic studies have suggested that patients with coronary artery disease who undergo exercise stress testing may demonstrate prolonged alterations of metabolism. For example, fluoro-deoxyglucose uptake may be increased in previously ischemic segments of the myocardium for at least 1 hour after exercise.⁸

There are several lines of evidence suggesting that stunned myocardium can occur in humans after thrombolytic therapy for acute myocardial infarction.^{1,9,10} There has been less evidence for stunned myocardium in humans when the episodes of ischemia are brief. A study by Wijns et al¹¹ showed that a form of stunned myocardium characterized by reduced ventricular compliance occurs after brief coronary artery occlusions in humans induced by angioplasty. Our study corroborates and extends the work of Robertson et al,⁵ suggesting that persistent regional wall motion abnormalities occur often after relatively brief episodes of exercise-induced ischemia in patients with coronary artery disease. Two-dimensional echocardiography is capable of detecting these zones of persistent left ventricular dysfunction, and involvement of several walls of the left ventricular is not uncommon. The percentage of patients having worse function at 15 or 30 minutes (95% and 90% respectively) was greater than immediately after exercise (73%). This raises the possibility that late

echocardiographic imaging after exercise stress testing may alter the sensitivity and specificity of the exercise test, but this concept will require further investigation. Our study was not designed to primarily test sensitivity and specificity of late echocardiographic imaging, especially since patients referred with coronary artery disease were a select group, i.e., the diagnosis was already known in many of the patients, and the degree and extent of narrowing were severe in many cases. Whether late imaging after exercise testing will be useful or will show stunning in a broader patient population with coronary artery disease needs to be determined. The length of time required for resolution of exercise-induced wall motion abnormalities is not known. In an ongoing study, we have observed persistent wall motion abnormalities in some patients for up to 45 minutes after exercise.

The reason that some patients exhibited worsened wall motion abnormality at 15 or 30 minutes compared with immediately after exercise is not clear. It is possible that at the very end of exercise, increased sympathetic output may mask regional wall motion abnormalities. Once the patient is at rest and there is less sympathetic tone the wall motion abnormalities may then emerge.

Recent studies suggest that epicardial coronary artery disease need not be present for stunned myocardium to develop. Experimentally hypertrophied ventricles without epicardial narrowing can develop prolonged dysfunction after exercise, presumably due to a relative imbalance between oxygen supply and demand at a microvascular level.¹² We have now observed dysfunction after exercise at 15 or 30 minutes in 3 patients who had no epicardial coronary artery disease at catheterization. Two of these patients developed ST depression during the exercise test and 2 had a history of angina. These observations raise the possibility of either syndrome X or a cardiomyopathic process in these patients.

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Serial Antiarrhythmic Drug Treatment to Maintain Sinus Rhythm After Electrical Cardioversion for Chronic Atrial Fibrillation or Atrial Flutter

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The sequential use of different types of antiarrhythmic drugs may improve arrhythmia prognosis in chronic atrial fibrillation or flutter after successful electrical cardioversion. The rationale for serial treatment is that the arrhythmogenic mechanism may vary between patients, leading to different responses to 1 specific drug. To investigate this issue prospectively, 127 patients having chronic fibrillation or flutter exclusively, underwent serial drug treatment with flecainide (stage I) followed by sotalol or, if contraindicated, quinidine (stage II) and eventually amiodarone (stage III). Stages II and III were entered after electrical recardioversion for a recurrence during stages I or II, respectively. Calculated on an actuarial basis, the 2-year cumulative percentage of patients free of the arrhythmia increased from 31% after stage I to 63% at the end of serial treatment. To reach this result, a mean of 1.8 ± 0.8 cardioversions per patient were needed, with 53 patients progressing to stage II and 34 to stage III. Sixteen patients stopped serial treatment prematurely and 15 patients were considered to have intractable atrial fibrillation at the end of stage III. Incidence of proarrhythmia was low. Multivariate analysis disclosed that an older age, in combination with a large number of previous episodes of arrhythmia, a long previous duration of arrhythmia and presence of mitral valve disease, were predictive for medical refractoriness during serial treatment. It is concluded that serial treatment may improve arrhythmia prognosis in atrial fibrillation or flutter, with an acceptable incidence of proarrhythmic events.

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Despite prophylactic treatment with class I antiarrhythmic drugs, chronic atrial fibrillation or flutter have a high propensity to recur after electrical cardioversion.¹⁻⁶ To improve the long-term arrhythmia outcome, it seems rational to change the type of drug after a recurrence, since each subtype exerts specific actions. Class IA and 3 drugs may be effective if the arrhythmia depends on shortening of refractoriness. Class IC drugs may act by suppressing arrhythmogenic premature beats or by rate-dependent prolongation of refractoriness.⁷ Only a few studies have reported that sequentially changing the type of drug after a recurrence may improve arrhythmia prognosis.^{8,9} To investigate this issue prospectively, we performed serial antiarrhythmic treatment in patients referred for direct-current cardioversion. Serial treatment involved the use of different types of antiarrhythmic drugs, with repeat cardioversion after each relapse of chronic arrhythmia. Drugs used were flecainide (phase I), sotalol or quinidine (phase II) and amiodarone (phase III). The aims of this study were to establish the rate of preserved sinus rhythm with use of this approach and to characterize the patient with medically intractable atrial fibrillation or flutter despite serial treatment.

METHODS

Patients: Between February 1986 and June 1989, 186 consecutive patients with chronic atrial fibrillation or atrial flutter underwent successful cardioversion to sinus rhythm using direct-current electrical cardioversion. The general outline of our protocol for cardioversion has been described previously.¹⁰ After the cardioversion, all patients were considered candidates for prophylactic antiarrhythmic drug treatment. However, 59 patients were excluded from participation in the study. Exclusion criteria were (1) paroxysmal atrial fibrillation or flutter, (2) bifascicular block or bundle branch block with a QRS duration >0.16 second, (3) known sick sinus syndrome in the absence of an artificial pacemaker, (4) congestive heart failure or angina pectoris greater than class III according to the criteria of the New York Heart Association, and (5) severe systemic

TABLE I Characteristics of 127 Patients Beginning Serial Antiarrhythmic Drug Treatment

Age (years)	60 ± 12
Men (no.)	65 (51%)
Atrial fibrillation (no.)	103 (81%)
Underlying heart disease (no.)*	
Coronary artery disease	30 (24%)
Stable angina pectoris	12
Old myocardial infarction	9
After CABG/PTCA	12/1
Rheumatic valvular disease	30 (24%)
Mitral valve disease	50 (37%)
Stenosis/regurgitation	29/27
Aortic valvular disease	26 (21%)
Stenosis/regurgitation	8/21
Systemic hypertension	20 (16%)
Congenital heart disease	9 (7%)
Dilated cardiomyopathy	6 (5%)
Corrected hyperthyroidism	4 (3%)
"Lone" fibrillation/flutter	22 (17%)
Previous cardiac surgery	36 (28%)
CABG/valvular surgery	16/23
Arrhythmia history	
Duration before cardioversion (days) median/range	180/1–6840
Total duration (months) median/range	22/0.1–300
Previous arrhythmia episodes	
n = 1	55 (43%)
n = 2	51 (40%)
Antiarrhythmic drugs used before	
n = 0	88 (69%)
n = 1	22 (17%)
NYHA class I, II, III	56 (44%), 58 (46%), 13 (10%)
Diuretics	50 (37%)
ACE inhibitor	9 (7%)
Left atrial size	
Long-axis view (mm)	45 ± 7
Apical view (mm)	66 ± 8
Left atrial area (mm ²)	2,442 ± 548
LVEDD (mm)	50 ± 7
LVESD (mm)	35 ± 7

*More than 1 disease entity per patient.
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; LVEDD/LVESD = left ventricular end-diastolic and end-systolic diameters, respectively; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty.

disease. Patients with a healed myocardial infarction within 2 years before entry into the study also were excluded. Antiarrhythmic drugs administered before inclusion in the study were discontinued ≥ 5 half-lives before the first cardioversion. The study was approved by the local medical ethical committee, and before initiating phase I informed consent for participation in the study was obtained. Table I lists clinical characteristics. Echocardiographic left atrial area was determined with the following formula: $(0.5 \times \text{left atrial diameter in long-axis view}) \times (0.5 \times \text{left atrial diameter in apical view}) \times \pi$.

Definition of terms: Chronic atrial fibrillation or flutter was defined as repeatedly documented arrhythmia, without intercurrent sinus rhythm on routine 12-lead electrocardiograms recorded at consecutive outpatient visits before cardioversion. To exclude patients with paroxysmal (stress-induced) adrenergic atrial fibrillation during these visits, 24-hour Holter monitoring

was performed. Previous arrhythmia duration is duration of the last continuous episode of fibrillation or flutter preceding the first cardioversion of this study. Total arrhythmia duration is the episode lasting from the onset of attacks of documented atrial fibrillation or flutter until the cardioversion under evaluation.

Protocol for serial antiarrhythmic drug treatment:

After the cardioversion, 4 different antiarrhythmic drugs in 3 sequential stages were administered. In the first stage, we used the type IC drug flecainide (Tambacor®, Riker 3M) in a dose of 200 or 300 mg/day. We did not give quinidine as the first drug because it is associated with a relatively high incidence of adverse effects. We reasoned that this might limit the feasibility of serial treatment, because it would cause too many patients to advance to stage II merely because of adverse effects early in the course of serial treatment. In addition, when we started the present study, flecainide appeared to be well tolerated and potentially effective.^{11,12} In patients with atrial flutter, verapamil was used to prevent a rapid ventricular rate in the event of a recurrence.^{13–15} The second stage was entered in case of a recurrence or adverse effects during flecainide treatment. It consisted of 160 mg of sotalol (Sotacor®, Bristol-Myers Company) administered twice daily. If there was a contraindication to sotalol, we used an alternative drug. Although drug effects may differ in the patient after cardioversion,¹⁶ quinidine 750 mg (Kini-dine Durette®, Astra) twice daily was chosen. Considering it as a "last resort" stage II drug, we accepted its disadvantages. After cardioversion in stages I and II the initial 3 drug doses were administered in the hospital. If there was recurrence during stage II, patients entered the third stage. Stage I nonresponders with contraindications for both sotalol and quinidine entered stage III directly. Before repeat cardioversion, all patients underwent loading with amiodarone, 600 to 800 mg/day, for ≥ 4 weeks. Thereafter, patients continued to take 200 to 400 mg/day depending on the 1-month plasma concentrations of both amiodarone and desethylamiodarone. If plasma concentrations for both were >0.5 mg/liter, these were arbitrarily considered "therapeutic" and a recardioversion was attempted.

Follow-up: After discharge from the hospital, patients visited the outpatient department 1, 3 and 6 months after the last cardioversion and at 6-month intervals thereafter. At the follow-up visits, patients were questioned for arrhythmia symptoms and adverse effects of drug therapy. A 12-lead surface electrocardiogram was recorded to determine the rhythm.

End point of the study: The end points were arrhythmia recurrence or adverse effect not amenable to dose reduction during stage III.

Statistical analysis: Data are reported as mean \pm 1 standard deviation. Median values were used in case of

a nonuniform distribution of variables. For the comparison of 2 groups, continuous normally distributed variables were tested by the 1-way analysis of variance. Variables with an asymmetric distribution were tested with the Mann-Whitney U test. Frequencies were compared by the chi-square test for equality of proportions and for small numbers (<10) with Yates correction. The diagnostic value of several sets of variables for arrhythmia recurrence was analyzed by logistic regression. The model estimates the probability *p* of recurrence as: $\text{prob}(\text{recurrence}) = 1/(1 + e^{-Z})$ (see Appendix), where *Z* represents the independent predictor variables (including a constant term) estimated from the data by likelihood-ratio test. Predictor variables were selected by forward stepwise selection.

The estimated model was used to measure the probability of arrhythmia recurrence for each individual member of the sample. Patients were reclassified for success or failure, according to the calculated probability of intractability in relation to the chosen cutoff point. Any patient whose estimated probability was higher than the chosen cutoff point was predicted to be intractable; the converse holds for patients with a lower value. The proportion of correctly reclassified patients was considered a measure of the diagnostic reliability of the predictor variables.¹⁷

RESULTS

After successful electrical cardioversion, 127 patients entered stage I. Of these 127 patients, 16 (13%)

FIGURE 1. Actuarial 2-year arrhythmia-free episodes for all patients after the last cardioversion to sinus rhythm, calculated on intention-to-treat basis. The figures below the curves indicate the number of patients at risk.

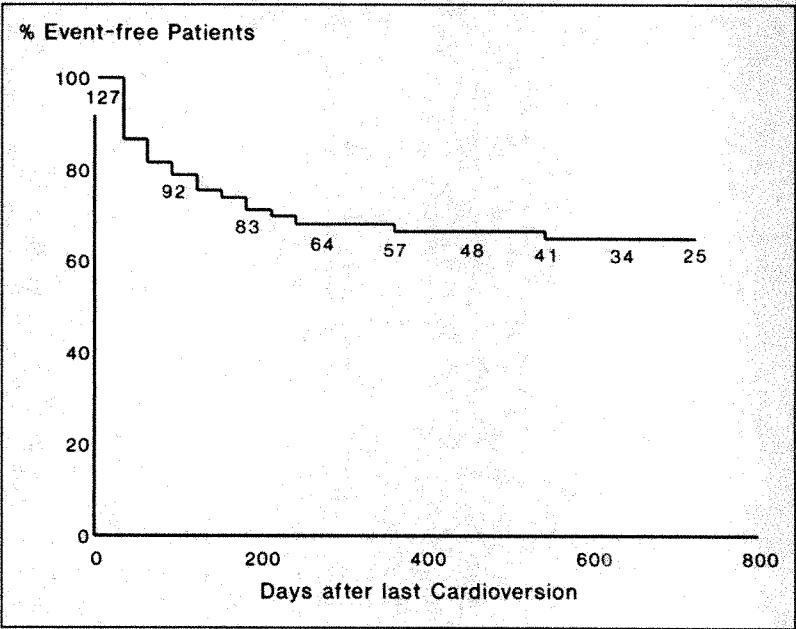


FIGURE 2. Actuarial 2-year arrhythmia-free episodes during the separate treatment stages. The figures below the curves indicate the number of patients at risk.

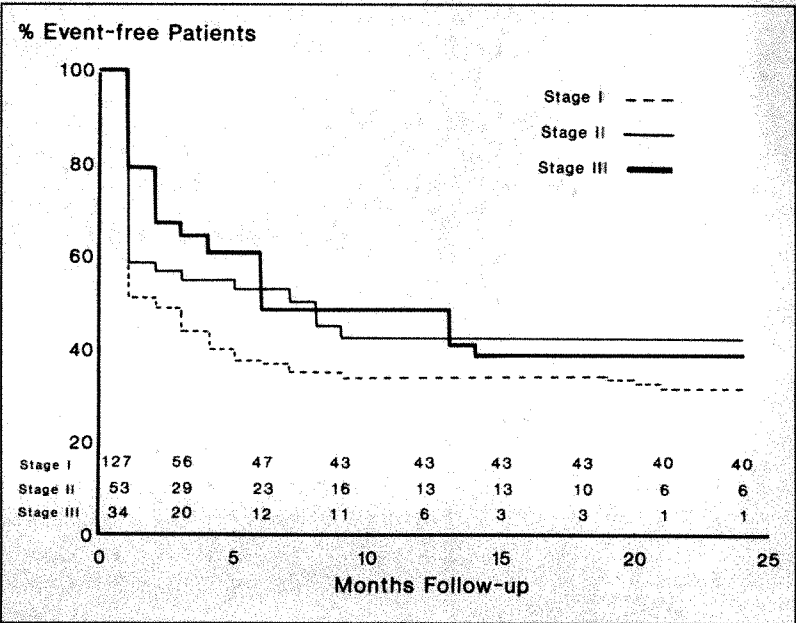


TABLE II Comparison of Patients Maintaining Sinus Rhythm and Patients Failing During Stage III: Univariate Analysis

	Sinus Rhythm	Arrhythmia Recurrence	p Value
No. of patients	81	15	
Age (years)	59 ± 12	65 ± 13	<0.05
Men (no.)	47 (58%)	7 (47%)	NS
Atrial fibrillation (no.)	65 (80%)	13 (87%)	NS
Underlying heart disease (no.)*			
Coronary artery disease	19 (24%)	6 (40%)	NS
Stable angina pectoris	8	3	
Old myocardial infarction	4	1	
After CABG	10	3	
Rheumatic valvular disease	14 (17%)	6 (40%)	NS
Mitral valvular disease	22 (27%)	9 (60%)	<0.05
Stenosis/regurgitation	16/12	7/5	
Aortic valvular disease	9 (11%)	5 (33%)	NS
Stenosis/regurgitation	2/7	1/4	
Systemic hypertension	17 (22%)	1 (7%)	NS
Congenital heart disease	8 (10%)	0 (0%)	NS
Dilated cardiomyopathy	3 (4%)	1 (7%)	NS
"Lone" arrhythmia	13 (16%)	1 (7%)	NS
Total duration (months)			
Median	13	58	<0.05
Range	1–230	17–162	
Previous arrhythmia episodes n ≥ 3	25 (31%)	13 (86%)	<0.05
NYHA class (no.)			
I	24 (29%)	2 (13%)	
II	46 (57%)	9 (60%)	NS
III	11 (14%)	4 (27%)	
Diuretics	27 (33%)	8 (53%)	NS
ACE inhibitor	7 (9%)	1 (7%)	NS
Left atrial size			
Long-axis view (mm)	44 ± 7	48 ± 6	NS
Apical view (mm)	66 ± 8	74 ± 4	<0.05
Left atrial area (mm ²)	2,329 ± 601	2,810 ± 526	<0.05

*More than 1 disease entity per patient.
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; NS = not significant; NYHA = New York Heart Association.

were prematurely withdrawn from serial treatment. Three patients died during the trial (2.4%) and 15 patients (12%) were considered to have intractable arrhythmia after stage III. On an intention-to-treat basis, the actuarial cumulative percentage of patients remaining in sinus rhythm for 1 and 2 years after the last cardioversion were 65 and 63%, respectively (Figure 1).

Stage I: After the first cardioversion, 127 patients received a mean dose of 210 ± 49 mg/day of flecainide, in a 2- or 3-times daily dosing scheme. Thirteen patients with atrial flutter were treated concomitantly with verapamil. Figure 2 shows the actuarial event-free intervals for all flecainide-treated patients. After 3, 12 and 24 months, 44, 34 and 31% of these patients were still in sinus rhythm. Two patients died during stage I. One patient with flutter, who had had a myocardial infarction 2 years previously, died suddenly 1 day after discharge. The other patient died from a massive acute myocardial infarction. Eight patients discontinued flecainide for adverse effects: 4 developed significant negative dromotropic effects and in 2 patients central nervous system symptoms necessitated cessation of the

drug. One patient had worsening of palpitations due to an increase in the number of ventricular premature beats. Finally, 1 patient, not known to have had ventricular arrhythmias, developed a hemodynamically significant ventricular tachycardia of 198 beats/min with sinusoidal QRS complexes 23 hours after initiation of 100 mg flecainide twice daily. Repeated electrical cardioversions were necessary, but recovery was uneventful.

After treatment was unsuccessful during stage I, 30 patients did not enter stage II of the trial: 2 patients died during stage I, 6 patients developed contraindications for treatment with antiarrhythmic drugs, and 10 were unwilling to continue the protocol. The remaining 12 patients entered stage III immediately after stage I for contraindications to treatment with sotalol or quinidine.

Stage II: In all, 53 patients entered stage II. Thirty-nine patients were treated with a daily dose of 269 ± 49 mg of sotalol and 14 with 1,500 mg of quinidine. After 3, 12 and 24 months, 55, 42 and 42% of these patients had preserved sinus rhythm (Figure 2). Adverse effects due to sotalol occurred in 5 patients and included facilitation of atrioventricular nodal tachycardias in 1 patient and congestive heart failure in a patient with a hypertrophic cardiomyopathy. The other 3 patients, respectively, had symptomatic sinus bradycardia, fatigue with dyspnea but without signs of congestive heart failure and intolerable diarrhea accompanied by headaches. Four patients taking quinidine developed unacceptable diarrhea.

Stage III: Thirty-four patients were treated chronically with 284 ± 151 mg/day of amiodarone. After loading with amiodarone, 4 patients (12%) converted to sinus rhythm without a repeat cardioversion. Figure 2 shows that after 3, 12 and 24 months, 64, 49 and 40% of patients treated with amiodarone had preserved sinus rhythm. Amiodarone was discontinued only in 2 patients because of skin photoallergy. No negative dromotropic effects were seen during amiodarone treatment. One patient, who had undergone coronary artery bypass grafting previously, died due to an acute myocardial infarction.

Intractable atrial fibrillation and flutter: To identify patients in whom cardioversion, per se, should be avoided because of intractability of the arrhythmia despite serial treatment, we compared all patients maintaining sinus rhythm with those unable to do so during stage III (Table II). Logistic regression analysis showed that age (regression coefficient 0.17, $p = 0.007$), number of previous episodes of arrhythmia (2.97, $p = 0.005$), total arrhythmia duration (0.026, $p = 0.004$) and presence of mitral valve disease (2.08, $p = 0.02$) were the best predictors for intractability. Although the left atrial size

discriminated significantly between responders and failures while evaluated univariately (Table II), this parameter was not taken into account in the logistic regression analysis because of too few cases available for evaluation, thereby potentially weakening the analysis.

To evaluate the diagnostic reliability of the predictor variables, 8 different classification rules for cutoff points from 0.8 to 0.1 were tested for their ability to discriminate between predicted and observed arrhythmia intractability. Table III shows sensitivity, specificity and post-test probability of intractability for the various cutoff points.

DISCUSSION

A recently performed meta-analysis indicated that after successful cardioversion, 50% of patients will have a recurrence of atrial fibrillation within 1 year, despite prophylactic treatment with quinidine.⁶ Up to now not many studies have addressed the issue of whether the arrhythmia prognosis may be improved by sequentially changing the type of drug after each recurrence of chronic arrhythmia.^{7,8} The present study is the first to suggest that such a strategy, in combination with electrical recardioversion in resistant cases, may reduce the recurrence rate from 50% to approximately 35%.

Comparison with previous studies: One retrospective study⁸ also evaluated the effects of serial drug treatment after repeat electrical cardioversion, with 1- and 2-year recurrence rates as high as 46 and 59%, respectively. In that study, only few patients relapsing for the second time underwent a third cardioversion. In addition, the relatively potent antiarrhythmic drug amiodarone¹⁸⁻²⁴ was not used.

In a prospective study, Antman et al⁹ studied the sequential use of propafenone and sotalol in patients with refractory atrial fibrillation or flutter. Paroxysmal atrial fibrillation was found in 50% of patients and relatively many patients classified as having chronic fibrillation (27%) converted to sinus rhythm merely after loading with sotalol. The latter characteristic may be especially regarded as favorably influencing the clinical behavior of the arrhythmia. Despite this, and notwithstanding the use of several drug dosages before considering the patient refractory, the 6-month recurrence rate still was 45%. Whether the use of a third agent, as in the present study, would have substantially improved outcome, remains a matter of speculation. However, the clinical applicability of a serial approach using many different agents may be limited because of dropouts.

Intractable atrial fibrillation and flutter: The results of this study may be used to identify the medically refractory patient beforehand. With the logistic regression equation, intractability despite amiodarone treat-

TABLE III Sensitivity, Specificity and Post-Test Probabilities of the Model at Eight Different Cutoff Points*

Cutoff Point	Sensitivity (%)	Specificity (%)	Post-Test Probability of Intractability (%)
0.8	21	100	100
0.7	36	99	83
0.6	43	98	75
0.5	57	96	73
0.4	57	94	62
0.3	79	89	55
0.2	86	86	52
0.1	93	78	24

*Sensitivity: the ability of the model to detect arrhythmia intractability despite serial treatment; specificity: the ability of the model to detect maintenance of sinus rhythm. Almost all intractable patients will be detected only at a low cutoff point, but at the cost of not selecting potential responders for serial treatment.

ment in stage III may be calculated using clinical characteristics like age, total arrhythmia duration, number of previous electrical cardioversions and type of underlying disease (see Appendix).

In clinical practice it is desirable to avoid serial treatment in intractable cases, and we advise one to use the cutoff point of 0.2, because this approach allows almost all patients with intractability to be detected (Table III). This does not dramatically affect the specificity of the presented model. However, the disadvantage is that, given a cutoff point of 0.2, approximately half (48%) of the patients not selected for cardioversion would have had benefit from serial treatment (1 - post-test probability of intractability). Fortunately, at the given cutoff point of 0.2, this applies only to a relatively low proportion of the potentially responding patient population (1 - sensitivity: 14%).

Studies with amiodarone in medically refractory patients variably identified previous arrhythmia duration^{20,21} and left atrial dimension^{20,22} as factors predicting outcome. In the present study, 4 different predictive factors were found. Discrepancies between studies are mainly caused by differences in data analysis, small patient numbers and inclusion of both paroxysmal and chronic fibrillation. The present investigation exclusively concerned chronic arrhythmia. Moreover, in contrast to most previous studies, our patient population was more homogeneous with respect to medical refractoriness since arrhythmia intractability was established prospectively in the course of serial treatment.

Comparison of drug efficacy: maintenance of sinus rhythm: Compared with the other drugs used in the present study, amiodarone was equally effective in maintaining sinus rhythm, even after failure with previous drugs. Apart from amiodarone being more potent, this may also have resulted from loading, although our loading regimen was rather conservative. For safety reasons,^{13,14,25-28} pretreatment to reach steady-state plasma concentrations was not instituted in stages I and

II. Amiodarone loading may have been especially useful in patients prone to very early recurrence. It also explains the difference in the pattern of recurrence. Whereas relapses with flecainide, sotalol or quinidine occurred predominantly within the first month, most relapses with amiodarone occurred only by the end of the second month.

Proarrhythmia: In the present study, only 1 patient had supraventricular proarrhythmia during sotalol (0.8%); however, in some cases recurrence may have been the result of atrial proarrhythmia.

A more serious problem is ventricular proarrhythmia during treatment of supraventricular arrhythmias.^{25,26,28,29} In this study, unexpected ventricular proarrhythmia was documented in 1 patient taking flecainide. Another patient taking flecainide, with an old myocardial infarction, died suddenly, presumably due to proarrhythmia.³⁰ Two other deaths were not related to the use of drugs. In their meta-analysis, Coplen et al⁶ showed that quinidine was associated with an increased total 1-year mortality (2.7%) compared with placebo or no treatment (0.6%). Total mortality in our study was 2.4%, comparable to that for patients receiving active treatment in the meta-analysis. However, in the studies evaluated,⁶ follow-up was relatively short. In addition, proarrhythmia-related mortality in the present study was only 0.8%, illustrating the relative safety of the agents used.

Other adverse effects: These occurred predominantly during the first 2 stages. The most frequent adverse effects with flecainide were due to the negative dromotropism. Because these patients were identified during the first stage and excluded from further study, this complication was infrequent during the next stages. In the second stage the most frequent adverse effect limiting drug treatment was diarrhea caused by quinidine. Amiodarone was remarkably well tolerated, which may be explained by the low dosage given.³¹⁻³³ In addition, patients were stringently advised to avoid excessive exposure to sunlight. Whether the long-term incidence of adverse effects stays low remains to be established, since it has been suggested that it is related to the cumulative dose.²⁴

Study limitations: The inclusion of a blinded placebo group would have strengthened this study. It would have answered the question of whether repeated cardioversions without institution of any prophylactic drug would have yielded the same result. However, inclusion of a placebo group in a blinded set-up would have meant withholding treatment considered to be effective. This was unacceptable from an ethical viewpoint. Also, we cannot tell from this study whether continuation of the same drug after every repeat cardioversion would have given a comparable arrhythmic outcome. How-

ever, drawing a parallel with the antiarrhythmic strategy in patients with sustained ventricular tachycardias or ventricular fibrillation, we believe that if a patient's condition does not improve with 1 specific type of antiarrhythmic drug, this agent should be abandoned, especially if the recurrence occurs very early after the cardioversion, which was the case in almost all recurrences.

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APPENDIX

The logistic regression model was used to uncover independent predictors for arrhythmia intractability despite serial treatment. It yielded a constant term and the variables age, previous episodes of arrhythmia, total arrhythmia duration and mitral valve disease. Previous episodes of arrhythmia and mitral valve disease are indicator variables, coded 0 or 1. The value 1 for previous episodes of arrhythmia indicates ≥ 3 episodes; the value 1 for mitral valve disease indicates presence of disease. Given these coefficients, the logistic regression equation for the probability of arrhythmia intractability can be written as: $\text{Prob}(\text{intractability}) = 1/(1 + e^{-Z})$, where $Z = -17.2148 + 0.1778(\text{age}) + 2.9714(\text{previous arrhythmia episodes}) + 0.0255(\text{total duration of arrhythmia}) + 2.0826(\text{mitral valve disease})$.

In applying this to a 65-year-old man with underlying mitral valve disease, with a total arrhythmia duration of 12 months, who also has had 3 previous episodes of chronic arrhythmia, then $Z = -17.2148 + 0.1778(65) + 0.0255(12) + 2.9714(1) + 2.0826(1) = -0.2978$. His pretest probability of arrhythmia intractability is then estimated to be $\text{Prob}(\text{intractability}) = 1/(1 + e^{-0.2978}) = 0.43$.

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Different Mechanisms of Polyuria and Natriuresis Associated with Paroxysmal Supraventricular Tachycardia

Takashi Fujii, MD, Shunichi Kojima, MD, Masahito Imanishi, MD,
Tohru Ohe, MD, and Teruo Omae, MD

The mechanism of polyuria associated with paroxysmal supraventricular tachycardia (SVT) was investigated in 8 patients. SVT was induced artificially and sustained for 60 minutes. Urine and blood samples were collected every 30 minutes. During the latter half of SVT, urine flow increased twofold in the control subjects before SVT. Urinary sodium excretion increased significantly ($p < 0.01$) within 30 minutes after SVT. Urinary excretion of antidiuretic hormone (ADH) decreased ($p < 0.01$) during the latter half of SVT and increased ($p < 0.01$) after SVT, respectively. Plasma level of ADH did not change during SVT but increased ($p < 0.05$) after SVT. The concentration of plasma atrial natriuretic polypeptide (ANP) increased significantly ($p < 0.05$) before SVT ended. Urinary excretion of prostaglandin E_2 increased significantly ($p < 0.05$) after termination of SVT. The percent changes in the urinary excretion of prostaglandin E_2 were correlated ($r = 0.713$, $p < 0.001$) with those of ADH. There was also a correlation ($r = 0.6$, $p < 0.001$) between the percent changes in the urinary excretion of prostaglandin E_2 and those of sodium. Their findings suggest that the polyuria during SVT is attributed mainly to the inhibition of ADH release and that the natriuresis after SVT is due not only to the increased ANP but also to the increased renal prostaglandin E_2 probably stimulated by ADH.

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It is a well-known phenomenon that polyuria occurs during supraventricular tachycardia (SVT).^{1,2} Natriuresis is also often observed in patients with SVT. Recent studies have suggested that a decrease in arginine vasopressin, the antidiuretic hormone (ADH), is responsible for polyuria³ and that an increase in atrial natriuretic peptide (ANP) induces natriuresis during SVT.^{4,5} Recently, we and other investigators^{5,6} have observed that natriuresis, maximal excretion in urine, is observed after SVT ends. However, the ANP level in plasma peaks during SVT. Thus, the existence of another mechanism was suspected for SVT-induced natriuresis in addition to the mediation of increased plasma ANP. For the purpose of clarifying the detailed mechanism of polyuria associated with SVT, the possibility that renal prostaglandin E_2 ⁷ and other hormones might cause natriuresis associated with SVT was examined in the present study.

METHODS

Patients: The subjects of this study were 8 patients with SVT (3 men and 5 women) aged 25 to 60 years (mean 41). They had normal renal and liver functions, with no evidence of organic heart disease or systemic hypertension. Electrophysiologic studies showed evidence of atrioventricular reentrant tachycardia in 6 patients and atrioventricular nodal reentrant tachycardia in 2. Each patient gave informed consent for participation in the study.

Study design: Administration of all antiarrhythmic drugs was discontinued for at least 1 week before the study. From 9 P.M. on the day before the examination to completion of the test, 10% para-aminohippurate (5 ml/hour) and 0.9% saline (95 ml/hour) solutions were infused through the antecubital vein. At 9 A.M. on the following day, the patients were asked to void their bladder before the examination. Then, they lay supine throughout the study except during urination. After the 60-minute control period, SVT was induced by programmed cardiac stimulation via an esophageal lead and sustained for 60 minutes. SVT was terminated by rapid atrial pacing through the same esophageal lead. Various parameters were measured for 60 minutes after termination of SVT. Blood pressure and heart rate

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were checked every 30 minutes with a mercury sphygmomanometer and by electrocardiography, respectively. Blood samples were taken every 30 minutes from 60 minutes before induction of SVT to 60 minutes after termination of SVT through a cannula inserted into a vein in the arm. Urine was collected by free voiding every 30 minutes simultaneously with blood samples.

Measurement of parameters in plasma and urine:

Osmolality was measured by a Fiske osmometer, electrolyte and creatinine concentrations by an autoanalyzer and para-aminopipprate concentration by the method of Smith et al.⁸ Blood for assaying ANP was transferred to a chilled tube containing ethylenediamine tetraacetic acid and was centrifuged. Plasma was stored at -80°C until it was assayed. Plasma ANP was measured by radioimmunoassay as reported by Kojima et al.⁹ ADH in plasma and urine was measured by radioimmunoassay as reported elsewhere.¹⁰⁻¹² Plasma renin activity was measured by radioimmunoassay using commercial kits (Dinabot).

Urinary prostaglandin E_2 levels were also measured in 7 patients by radioimmunoassay in accordance with the assay procedure for a commercial kit which uses ^{125}I as a tracer (New England Nuclear Corporation, Boston, Massachusetts). Catecholamine levels were measured by the fluorimetric method.

Statistical analysis: Statistical assessment of the data was done by randomized block analysis of variances with the mean of 2 values measured before onset of SVT as the control value. A Student Newman-Keuls test was used for simultaneous multiple comparison. The results are expressed as mean \pm standard error of the mean. Considering the differences between sexes, we evaluated urinary prostaglandin E_2 on the basis of

the percentage of urinary prostaglandin E_2 with the control period value as 100%. The relations between 2 variables were examined by the least-squares method.

RESULTS

Changes in hemodynamics: Mean heart rate, blood pressure, urine volume and urinary sodium excretion at different times are shown in Figure 1. The heart rate increased ($p < 0.01$) during SVT. Systolic blood pressure decreased ($p < 0.01$) during tachycardia and diastolic blood pressure tended to decrease, although insignificantly. Both heart rate and blood pressure returned almost to control values soon after termination of SVT.

Changes in urine and renal functions: Urine volume increased significantly ($p < 0.01$) from 1.89 ± 0.34 to 5.16 ± 1.03 ml/min during the second half of SVT and to 4.76 ± 0.77 ml/min in the early phase of recovery, and returned nearly to the control level in the final 30 minutes. Excretion of urinary sodium tended to decrease slightly from 248 ± 23 $\mu\text{Eq}/\text{min}$ during SVT, but increased significantly ($p < 0.01$) to 367 ± 47 $\mu\text{Eq}/\text{min}$ in the early phase of recovery (Figure 1). Similar to the changes in excretion of urinary sodium, fractional excretion of sodium also increased significantly ($p < 0.05$) in the early and late phases of recovery (Table I). Creatinine clearance tended to increase from the second half of SVT to 30 minutes after termination of SVT, whereas para-aminohippurate clearance showed a tendency to decrease. Filtration fraction increased significantly ($p < 0.01$) during SVT (Table I). Urinary osmotic pressure decreased significantly ($p < 0.01$) during SVT, corresponding to the peak time of urine volume, whereas free water clearance increased ($p < 0.01$). Hypotonic urine persisted for 30 minutes af-

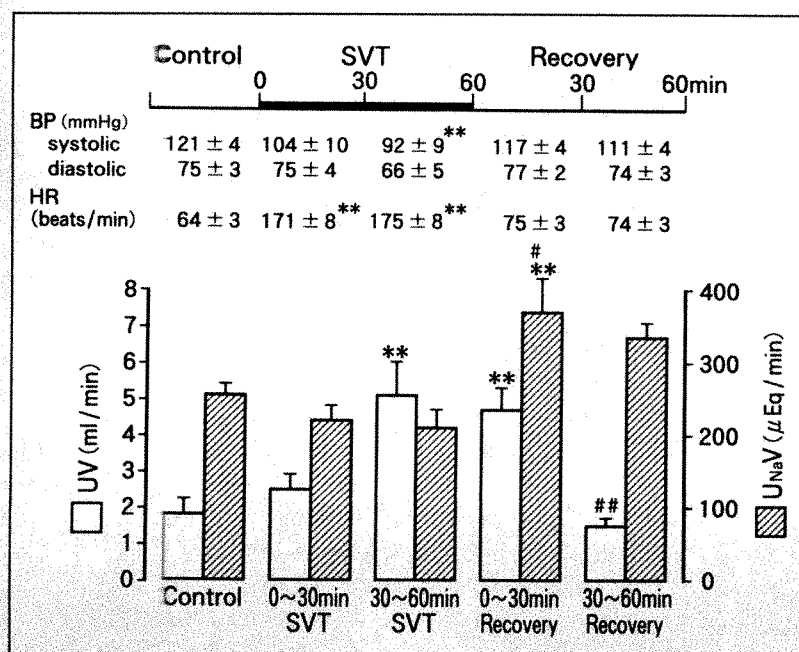


FIGURE 1. Changes in blood pressure (BP), heart rate (HR), urinary volume (UV) and urinary sodium excretion (UNaV). Values are mean \pm standard error of the mean. $^{**}p < 0.01$ compared with control values; $^{\#}p < 0.05$ and $^{\#}p < 0.01$ compared with values obtained during the latter half of supraventricular tachycardia (from 30 to 60 minutes). SVT = supraventricular tachycardia.

TABLE 1 Changes in Renal Functions and Catecholamines in Plasma During and After Supraventricular Tachycardia

	Control	SVT (minutes)		Recovery (minutes)	
		0-30	30-60	0-30	30-60
Creatinine clearance (ml/min/m ²)	119 ± 10	127 ± 16	139 ± 22	132 ± 15	112 ± 10
p-aminohippurate clearance (ml/min/m ²)	391 ± 34	333 ± 54	312 ± 44	393 ± 33	406 ± 54
Filtration fraction	0.32 ± 0.03	0.40 ± 0.03*	0.45 ± 0.04†	0.34 ± 0.03‡	0.29 ± 0.03‡
Fractional excretion of sodium (%)	1.41 ± 0.13	1.30 ± 0.22	1.05 ± 0.25	1.93 ± 0.28*	2.08 ± 0.31*‡
Plasma renin activity (ng/ml/hour)	1.4 ± 0.4	1.9 ± 0.4	3.2 ± 0.9†	1.5 ± 0.4	1.2 ± 0.3‡
Plasma noradrenaline concentration (pg/ml)	285 ± 34	414 ± 57*	455 ± 62*	318 ± 44	331 ± 48§
Plasma adrenaline concentration (pg/ml)	28 ± 9	34 ± 11	38 ± 13	26 ± 7	29 ± 9

*p < 0.05; †p < 0.01 compared with control values; §p < 0.05; ‡p < 0.01 compared with values obtained during the latter half of supraventricular tachycardia (from 30 to 60 minutes).

Values are mean ± standard error of the mean.

ter termination of SVT but returned to the control value in the next 30 minutes (Figure 2). Serum osmotic pressure did not change significantly during and after SVT.

Changes in urinary and blood hormones: The plasma levels of ADH, which were 2.4 ± 0.6 pg/ml in the control period and 2.2 ± 0.7 pg/ml during the second

half of SVT, increased significantly ($p < 0.01$) to 3.8 ± 1.0 pg/ml in the early phase of recovery (Figure 3). Urinary excretion of ADH decreased significantly ($p < 0.01$) from 30 ± 11 to 8 ± 2 pg/min in the latter half of SVT and increased significantly ($p < 0.01$) to 74 ± 15 and 125 ± 41 pg/min in the early and late phases of recovery, respectively (Figure 4). The plasma

FIGURE 2. Changes in urinary osmolality (Uosm), free water clearance (CH₂O) and osmolar clearance (Cosm). Values are mean ± standard error of the mean. **p < 0.01 compared with control values. SVT = supraventricular tachycardia.

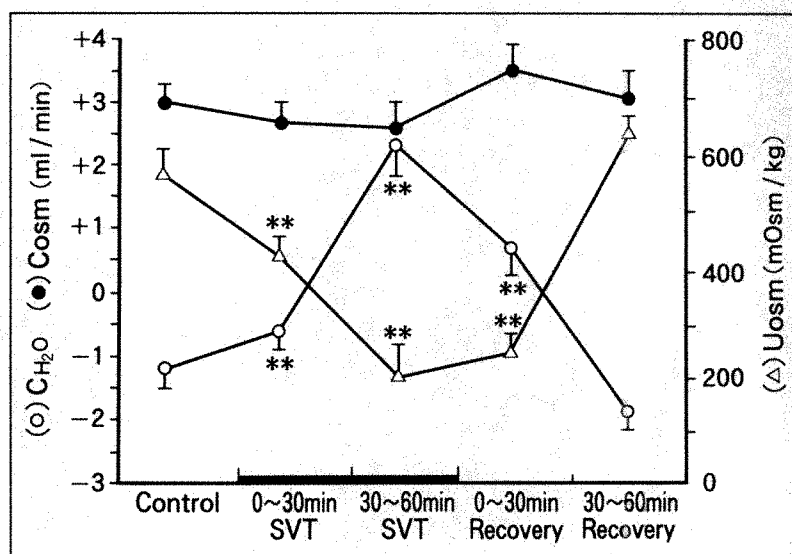
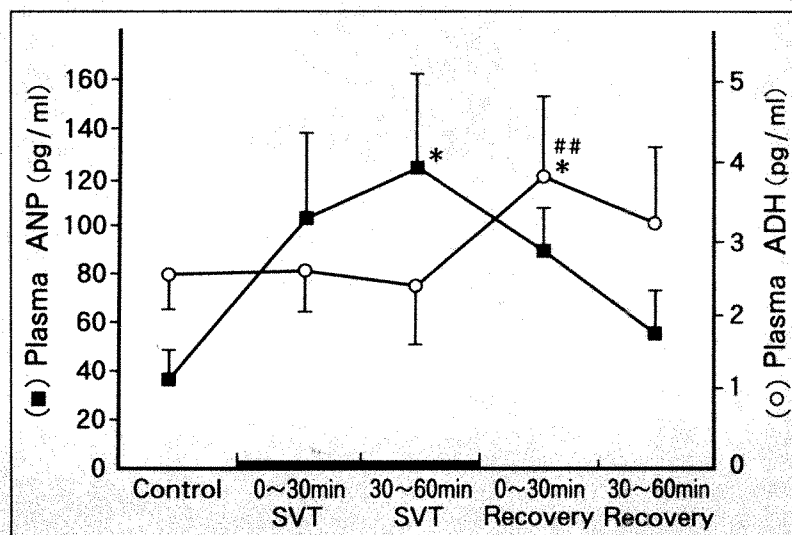


FIGURE 3. Changes in plasma concentrations of atrial natriuretic polypeptide (ANP) and antidiuretic hormone (ADH). Values are mean ± standard error of the mean. *p < 0.05 compared with control values; ##p < 0.01 compared with values obtained during the latter half of supraventricular tachycardia (from 30 to 60 minutes). SVT = supraventricular tachycardia.



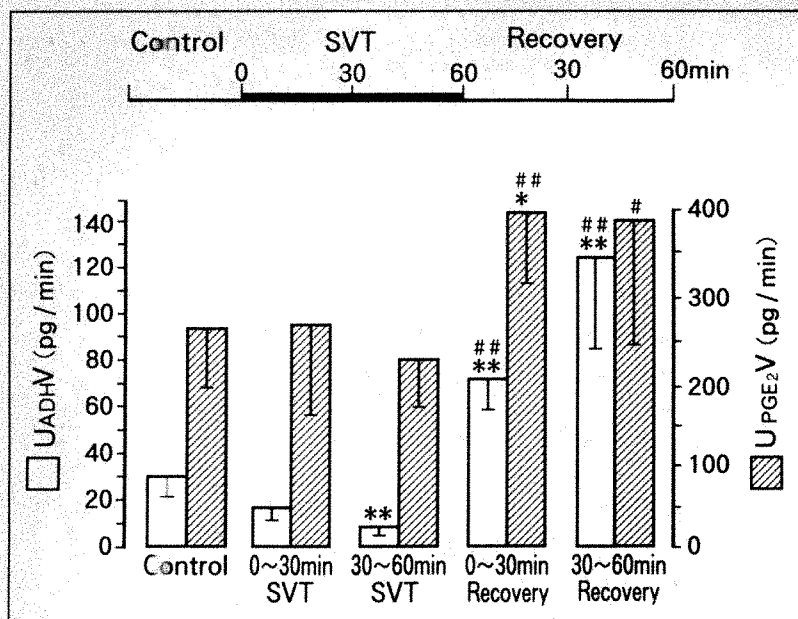


FIGURE 4. Changes in urinary excretion of antidiuretic hormone (UADHV) and prostaglandin E₂ (UPGE₂V). Values are mean \pm standard error of the mean. * $p < 0.05$ and ** $p < 0.01$ compared with control values; # $p < 0.05$ and ## $p < 0.01$ compared with values obtained during the latter half of supraventricular tachycardia (from 30 to 60 minutes). SVT = supraventricular tachycardia.

levels of ANP increased significantly ($p < 0.05$) from 37 ± 13 to 127 ± 43 pg/min in the second half of SVT and returned to the control level 1 hour after termination of SVT (Figure 3). Urinary excretion of prostaglandin E₂ tended to be slightly suppressed during SVT, but increased significantly ($p < 0.05$) from 259 ± 79 to 396 ± 84 pg/min in the early phase of recovery (Figure 4). There were significant correlations

between the percent changes in urinary excretion of ADH and prostaglandin E₂ and between those in urinary excretion of prostaglandin E₂ and sodium (Figure 5). Plasma renin activity increased significantly ($p < 0.01$) in the second half of SVT and plasma noradrenaline concentration increased significantly ($p < 0.05$) during SVT (Table I), although there was no significant change in adrenaline concentration.

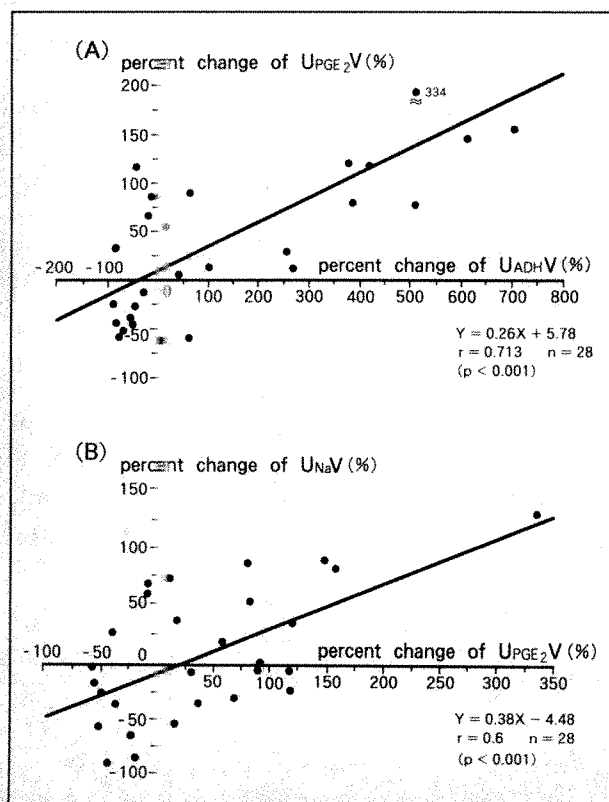


FIGURE 5. (A) correlation between urinary excretion of antidiuretic hormone (UADHV) and urinary excretion of prostaglandin E₂ (UPGE₂V). (B), correlation between UPGE₂V and urinary sodium excretion (UNaV).

DISCUSSION

Our study clearly showed polyuria during SVT and natriuresis after SVT. The urine obtained in this polyuric phase was hypotonic. The increase in urine volume was attributed to the increase of both water diuresis and osmolar clearance. The ratio of the increase in free water clearance to urine volume was found to be 80 to 90%. Therefore, the increase in urine volume was mostly due to increase in water diuresis, and osmolar clearance had little to do with this increase.

Despite the decrease in urinary excretion of ADH, the plasma levels of ADH did not change significantly during tachycardia. This discrepancy may be because (1) the rate of plasma ADH adhesion to platelets is as high as 90% in plasma,¹³ (2) various types of proteases contained in blood are likely to decompose ADH, and (3) secretion of plasma ADH is affected by body position, stress, and so forth. Thus, it is possible that blood sampling at a single point of time does not adequately reflect secretion of ADH. Therefore, to assess the amount of ADH release, measurement of urinary ADH appears to be more accurate than that of plasma ADH.

Plasma level of ADH is regulated by osmoreceptors,¹⁴ which exist mainly in the hypothalamic anterior wall or the third ventricle. It is also regulated by stretch receptors^{15,16} in the left atrium or the carotid sinus.

Boykin et al¹⁷ showed that rapid atrial pacing in dogs causes diuresis and suppression of ADH in plasma and that the effects are abolished by bilateral cervical vagotomy. Therefore, when left atrial pressure increases, the atrial stretch receptors with vagal afferents to the hypothalamus tonically inhibit the release of ADH and probably cause diuresis.¹⁸

Thus, our data suggest that polyuria associated with SVT is water diuresis due to suppression of ADH release as suggested by other investigators.^{3,16} Natriuresis was observed only in the early recovery phase. Therefore, some hormones inducing natriuresis were examined.

ANP is a polypeptide with a strong natriuretic action.¹⁹⁻²¹ It is well known that extensive stimulus due to elevation in atrial pressure causes an increase in the plasma ANP level during SVT or other types of tachycardia.³ However, many points still remain controversial as to the effect of ANP on renal hemodynamics²² and especially the mechanism of natriuresis. In our present study, the plasma ANP level increased significantly before SVT ended. The glomerular filtration rate tended to increase and the filtration fraction increased in the kidney during SVT, although the renal plasma flow tended to decrease (see Table I). Our finding is consistent with the report of Marin-Grez et al,²³ that ANP induces a postglomerular vasoconstriction accompanied by a preglomerular vasodilation in rat kidney. Sosa et al²⁴ reported that the natriuretic effect of ANP disappeared in dogs with hypotension. In our study, hypotension was also observed, and this is considered to be one of the reasons why natriuresis was not observed during SVT. Weidmann et al²⁵ reported that transient ANP infusions in humans produced natriuresis that continued after plasma levels of ANP had returned to baseline. One should also consider that the natriuresis observed after SVT may have resulted from elevations in ANP during SVT and recovery of hemodynamic factors.

After the termination of SVT, ADH in both plasma and urine increased. The acute elevation in left atrial pressure during SVT causes the suppression of ADH release, but the sudden normalization in pressure after SVT and the persistent water diuresis during SVT may cause a postsuppression increase in ADH as a rebound effect. ADH was reported to stimulate the renal synthesis of prostaglandin E₂,^{7,26} which is produced mainly in the medulla and causes natriuresis.^{27,28} The natriuretic action of prostaglandin E₂ is independent of the effects of ANP.^{7,29} This prostaglandin E₂ may modulate the antidiuretic action of ADH via a closed feedback loop.²⁸ In the present study, urinary excretion of prostaglandin E₂ increased after SVT and was correlated with urinary excretion of ADH. There was also a correlation between urinary prostaglandin E₂ and sodium

excretion. Thus, renal prostaglandin E₂, the biosynthesis of which may be stimulated by an increase in plasma ADH, should increase sodium excretion. There is a possibility that natriuresis after SVT is closely related to the increase in ADH-mediated prostaglandin E₂.

Plasma renin activity or catecholamines did not decrease during and after SVT. Therefore, suppression of the renin-angiotensin system or the sympathetic nervous system can hardly be considered as the mechanism of natriuresis in this study.

These findings demonstrate that polyuria during SVT is attributed mainly to the inhibition of ADH release and that the natriuresis after SVT is due not only to the increased ANP, but also to the increased renal prostaglandin E₂ probably stimulated by ADH.

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Effect of Reflex Vagal Activation on Frequency of Ventricular Premature Complexes

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To evaluate the antiarrhythmic effect of reflex-induced vagal activation, phenylephrine was infused in 17 patients with frequent ventricular premature complexes (VPCs). The role of heart rate reduction in suppressing VPCs was explored by pacing the atria at the preinfusion levels. Baroreceptor activation was considered effective when a $\geq 20\%$ decrease in heart rate was observed. Ten patients (59%) achieved the target heart rate decrease ($-29 \pm 5\%$), whereas in 7 (41%) the baroreceptor reflex was considered inadequate. In the former group ("responders"), heart rate decreased from 73 ± 7 to 52 ± 6 beats/min ($p < 0.0001$). When heart rate was allowed to fluctuate, ectopic activity was completely abolished in 9 of 10 patients; mean number of VPCs decreased from 38 ± 8 to $0.2 \pm 0.6/100$ beats ($p < 0.0001$). During pacing, VPCs reappeared but their mean number ($22 \pm 10/100$ beats) was still significantly reduced compared with control values ($p = 0.003$). In the "nonresponders," despite adequate blood pressure increases, VPC frequency was not affected. The QT interval lengthened during phenylephrine (392 ± 17 ms) versus control conditions (372 ± 18 ms, $p = 0.0008$) in the responders group, whereas no change was observed in the nonresponders.

These results demonstrate that reflex vagal activation markedly reduces VPCs. This effect is only partially rate-dependent; direct and indirect electrophysiologic changes secondary to baroreflex activation are also likely to be involved.

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Experimental and clinical data support the concept of an antiarrhythmic effect of vagal activation on ventricular arrhythmias.¹⁻⁷ Waxman and Wald provided the first reports that vagal activation, reflex-induced by phenylephrine injection or carotid sinus massage, could terminate ventricular tachycardia⁵ and could slow idioventricular rhythm.⁶ A negative chronotropic effect at ventricular level had been already obtained by acetylcholine and vagal stimulation in dogs with heart block.^{8,9}

To better understand the mechanisms underlying the antiarrhythmic action of increased vagal activity, we studied the effects of reflex-induced parasympathetic activation in patients with chronic ventricular arrhythmias having very frequent ventricular premature complexes (VPCs).

Previous studies involved carotid sinus massage¹⁰ or phenylephrine infusion.¹¹ However, their interpretation was hampered by the fact that the decrease in VPC rate was always preceded or accompanied by a reduction in heart rate, a factor that may be antiarrhythmic.¹²⁻¹⁴

The present clinical study had 2 main objectives. The first was to assess quantitatively the effect of reflex-induced vagal activation, obtained by phenylephrine infusion, in suppressing frequent VPCs in patients with chronic ventricular arrhythmias. The second was to draw inferences on the mechanisms involved, controlling heart rate by means of atrial pacing.

METHODS

Study group: The population under study consisted of a selected patient group with highly frequent and stable VPCs as assessed by 2 consecutive 24-hour Holter recordings. Only patients with >600 VPCs/hour and with $<30\%$ degree of VPC variability between daytime hours were admitted to the study. Patients were evaluated by noninvasive procedures (complete clinical evaluation, exercise stress testing, 2-dimensional echocardiogram). Exclusion criteria included depressed myocardial function (left ventricular ejection fraction $<50\%$), unstable angina and recent myocardial infarction, atrial flutter or fibrillation, sinus node dysfunction, atrioventricular block, arterial hypertension, and chronic use of any drug that could interfere with

TABLE I Patient Characteristics

	Responders	Nonresponders
Number of patients	10	7
Mean age (years)	43 ± 12 (24–64)	60 ± 8 (49–72)
Men/women	6/4	4/3
Heart disease:		
None	6	2
Coronary	1	1
Mitral valve prolapse	2	1
Systemic hypertension	1	1
Mitral stenosis	—	1
Congestive cardiomyopathy	—	1
Arrhythmia		
VPCs/hour	1,481 ± 450	1,308 ± 510
Couplets/24 hours	1,147 ± 1,242	176 ± 330
Nonsustained VT/24 hours	83 ± 99	2 ± 3

VPCs = ventricular premature complexes; VT = ventricular tachycardia.

sinus node function. All patients gave informed consent for the study.

Study protocol: The test was always performed in the morning, 2 hours after a light breakfast, while the patient was lying supine. The electrocardiogram (leads I, II, V₁) was continuously recorded on a Gould ES 1000 polygraph recorder and blood pressure was determined with a standard cuff manometer every 3 minutes. A slow intravenous infusion of saline solution was begun and a pill bipolar electrode for transesophageal atrial pacing was positioned. Pacing parameters were 10 to 20 ms in duration and 10 to 15 mA in intensity. In 2 patients, who complained for epigastric discomfort during pacing, a bipolar intracavitary electrode was positioned via the basilic vein and advanced into the right atrium.

After 5 to 10 minutes allowed for stabilization, the electrocardiogram was recorded for a baseline period of 10 minutes. Phenylephrine infusion (70 µg/ml saline solution) was then started at 20 µg/min and increased stepwise (20 µg/min) every 5 to 8 minutes to obtain a gradual increase in blood pressure. Reflex vagal activation was considered effective when a ≥20% decrease in heart rate was observed. Patients who did not achieve this target, despite maximal phenylephrine infusion (200 µg/min) or 40-mm Hg increase in mean blood pressure, were defined as nonresponders. When a steady-state VPC suppression was observed for ≥2 consecutive minutes, atrial pacing was begun at the preinfusion rate and maintained for 3 minutes. During pacing, phenylephrine infusion was held constant. Pacing was performed by an A.I.S. 4279 stimulator (Devices Limited, Hatfield, United Kingdom) with a pulse duration of 10 to 20 ms and an intensity of 12 to 20 mA.

Data analysis: For each of the 3 periods (baseline, bradycardia secondary to baroreceptor activation, atrial pacing) the following variables were analyzed: (1) VPC

rate, expressed as number of VPCs/100 beats; (2) coupling intervals of the ectopic beats to the preceding sinus or paced beat; and (3) QT interval. The QT interval was measured in control conditions, while the patient was in sinus rhythm, and during phenylephrine infusion, while the baseline heart rate was restored by atrial pacing. With the same heart rate, there was no need to use the traditional correction formulas (e.g., Bazett's) and the results are expressed as QT measured. Measurements were performed by an investigator who had no knowledge of the case. The same lead allowing a precise evaluation of the end of the T wave, usually lead II, was used at a paper speed of 25 mm/s. At least the first 3 beats following a VPC were not considered for the analysis; the reported value is the average of 5 measurements in nonconsecutive beats.

Statistical analysis: The Fisher exact test was used to analyze discrete variables. Analysis of variance for repeated measures was performed to analyze the effect of phenylephrine, during both sinus rhythm and atrial pacing, on VPC frequency. Student's *t* test for paired and unpaired data (2-tailed) was applied to compare continuous variables before and after phenylephrine infusion and between responders and nonresponders. A *p* value <0.05 was regarded as significant. The Bonferroni method for the limitation inherent in multiple pairwise comparisons was applied.¹⁵ Data are reported as mean ± standard deviation unless otherwise specified.

RESULTS

Patient characteristics: The study group consisted of 17 patients (10 men and 7 women, mean age ± standard deviation 50 ± 14 years [range 24 to 72]). In 7 of the 17 (41%), baroreceptor activation was considered inadequate because heart rate reduction during phenylephrine therapy was <20% (mean 7 ± 7%). These patients were defined as nonresponders and did not undergo atrial pacing. Ten patients (59%), defined as responders, achieved the target decrease in heart rate (mean 29 ± 5%) and underwent the entire protocol. The clinical characteristics of the 2 groups are listed in Table I. The only significant difference was age, since responders were younger than nonresponders (43 ± 12 vs 60 ± 8 years, *p* <0.01).

Effect of phenylephrine in responders: This group of 10 patients had frequent ectopic activity during Holter monitoring (mean 25 VPCs/min, range 12 to 34); in 9 of 10 patients couplets or salvos of nonsustained ventricular tachycardia or both, were present (Table I). The coupling interval of ectopic beats was 495 ± 55 ms. During the 10-minute control period, heart rate was 73 ± 7 beats/min and the number of VPCs/min was 27 ± 6, a value similar to the mean value observed during Holter recording.

TABLE II Effect of Phenylephrine (Phe) Infusion on Systolic Blood Pressure, Heart Rate, Number of Ventricular Premature Complexes per 100 Beats, Coupling Interval and QT Interval in the Responders (n = 10)

	Control (A)	Phe (B)	Phe + Pacing (C)	p Values	
				A vs B	A vs C
Blood pressure (mm Hg)	130 ± 19 (108–175)	161 ± 22 (130–210)	160 ± 22 (130–210)	<0.0001	<0.0001
Heart rate (beats/min)	73 ± 7 (57–84)	52 ± 6 (42–60)	74 ± 7 (60–85)	<0.0001	NS
Ventricular premature complexes (n%)	38 ± 8 (23–50)	0.2 ± 0.6 (0–2)	22 ± 10 (0–33)	<0.0001	0.003
Coupling interval (ms)	495 ± 55 (420–600)	—	481 ± 49 (440–612)	—	NS
QT interval* (ms)	372 ± 18 (350–404)	—	392 ± 17 (359–414)	—	0.0008

*Note that for each patient in A and C, heart rates were identical. Values are expressed as mean ± standard deviation; the range is indicated in parentheses. NS = not significant.

Phenylephrine increased systolic blood pressure from 130 ± 19 to 161 ± 22 mm Hg (+24%) and diastolic blood pressure from 80 ± 7 to 102 ± 14 mm Hg (+27%), whereas heart rate decreased from 73 ± 7 to 52 ± 6 beats/min (−29%). During the reflex bradycardia, ectopic activity was completely suppressed (100%) in 9 of 10 subjects; it was reduced by 94% in the remaining patient. The mean number of VPCs decreased from 38 ± 8 to $0.2 \pm 0.6/100$ beats (Table II).

Atrial pacing partially reverted this antiarrhythmic effect in 8 of 10 patients, whereas arrhythmia suppression remained >80% compared with control values in 2 patients (Figure 1). Mean VPC rate during pacing increased to $22 \pm 10.5/100$ beats ($p < 0.0001$) but remained still significantly suppressed compared with baseline values (−42%, $p = 0.003$, Table II). Two examples are shown in Figures 2 and 3. The coupling intervals of VPCs remained unchanged (481 ± 49 vs 495 ± 55 , $p =$ not significant).

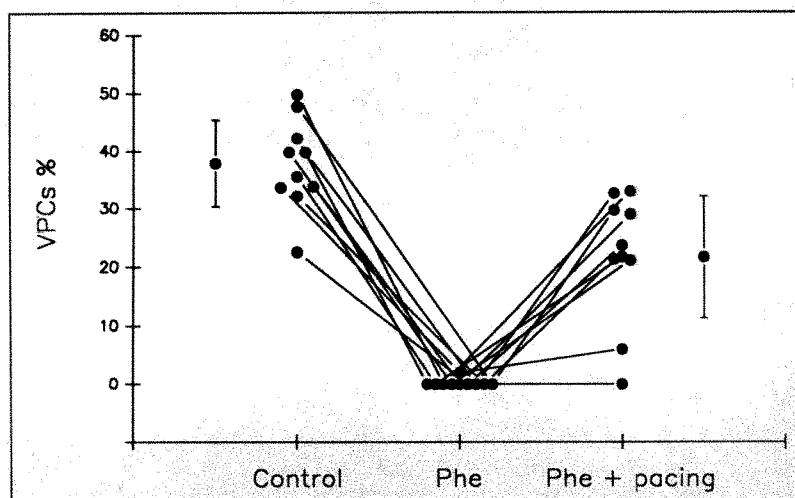
The QT interval significantly prolonged during phenylephrine compared with baseline values (392 ± 17 vs 372 ± 18 ms, +5.4%, $p = 0.0008$).

After cessation of the infusion of phenylephrine, VPCs reappeared within 2 to 4 minutes. Their mean number was $39 \pm 10/100$ beats and did not differ from baseline values.

Effect of phenylephrine in nonresponders: This group of 7 patients showed frequent ectopic activity during both Holter recording (22 ± 8 VPCs/min) and the 10-minute control period before phenylephrine infusion (21 ± 5 VPCs/min). Baseline systolic blood pressure (147 ± 20 mm Hg) and heart rate (80 ± 13 beats/min) did not differ significantly from the values observed in the responders.

During phenylephrine infusion (113 ± 49 μ g/min), systolic blood pressure increased from 147 ± 20 to 188 ± 25 mm Hg (+28%, $p < 0.0001$) and diastolic blood pressure from 84 ± 7 to 99 ± 9 mm Hg (+18%, $p < 0.001$), but heart rate decreased only slightly from 80 ± 13 to 74 ± 11 beats/min (−7%, $p = 0.06$). The mean number of VPCs did not change (25 ± 14 during phenylephrine vs 26 ± 6 in control condition, $p = 0.84$). No patient had VPCs completely abolished; however, they were reduced by >80% in 2 patients whose heart

FIGURE 1. Effect of phenylephrine infusion on ventricular premature complexes (VPCs) in the responders. Each circle represents the number of VPCs/100 beats in the single patient during baseline (Control), after phenylephrine infusion when both heart rate is allowed to decrease (Phe) and is held constant by pacing (Phe + pacing). The 2 circles with bars represent the mean values ± standard deviation in control conditions and during pacing.



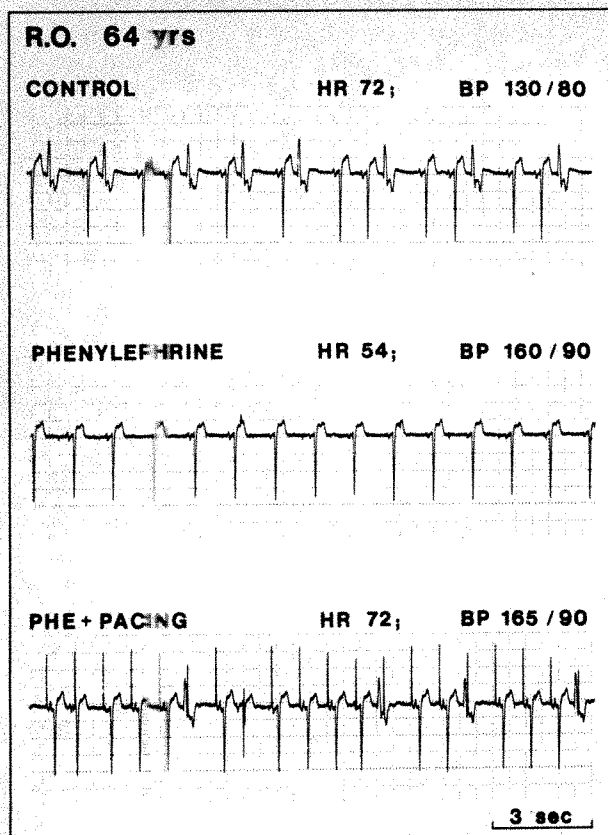


FIGURE 2. Ventricular bigeminy and trigeminy in a patient with ischemic heart disease. During baroreflex-induced bradycardia, ventricular premature complexes were abolished but reappeared, although less frequently, when pacing was performed. *Bottom strip*, some atrial premature beats are present. BP = blood pressure; HR = heart rate; PHE = phenylephrine.

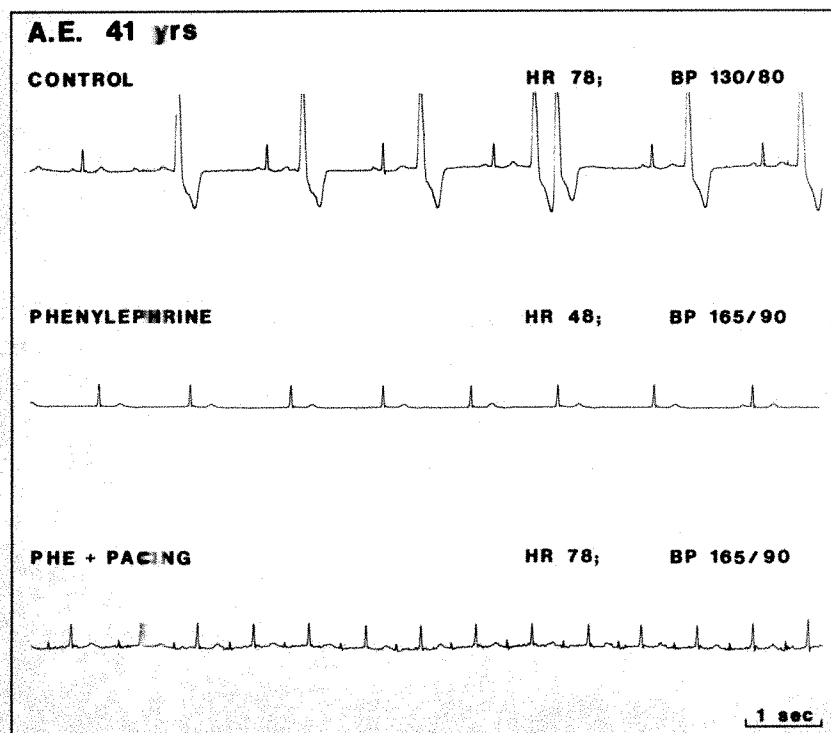


FIGURE 3. Frequent monomorphic ventricular premature complexes in a patient without apparent heart disease. During reflex bradycardia (48/min), ventricular premature complexes were abolished, and also remained suppressed when heart rate (HR) was restored to the control levels. In the *second strip* the dominant rhythm is junctional. BP = blood pressure; PHE = phenylephrine.

rate decreased by 12 and 19%, the latter being just 1 beat/min short for the eligibility criteria established for the responders group.

The QT interval, at variance with what was observed among responders, remained unchanged in these patients (368 ± 22 ms during phenylephrine vs 369 ± 28 ms during baseline). The different behavior of the QT interval in the 2 subgroups of patients is shown in Figure 4.

DISCUSSION

This study has demonstrated that phenylephrine infusion may cause suppression of VPCs. This antiarrhythmic effect is dependent on the activation of the baroreceptor reflex. The mechanisms involved are: (1) the reduction of heart rate, which plays an important but not an exclusive role, as proven by the results obtained with cardiac pacing; and (2) the electrophysiologic effects secondary to simultaneous vagal activation and sympathetic inhibition.

The baroreflex response induced by phenylephrine infusion mainly involves an increase in vagal activity at the cardiac level.^{16,17} The discussion will therefore focus on the antiarrhythmic mechanism of vagal activation.

Arrhythmia variability: The possibility that VPC suppression could simply be the result of spontaneous variability¹⁸ and not the consequence of the pharmacologic intervention was ruled out on the basis of several lines of evidence. First, mean VPC frequency was very high in each patient during both Holter recordings and

10-minute control recording before drug infusion. Second, spontaneous abolition of ectopic activity was never observed during the protocol both before onset of reflex vagal activation and after the washout of phenylephrine had been completed. Third, the antiarrhythmic effect vanished with disappearance of the physiologic effect of phenylephrine.

Role of the alpha-adrenergic effect of phenylephrine: VPC suppression was observed whenever a significant bradycardia, due to baroreceptor activation, occurred. No reduction in VPC number was achieved in patients whose heart rate was not reduced despite high doses of phenylephrine and significant blood pressure elevation. This observation indicates that the antiarrhythmic effect of phenylephrine is neither due to a direct α -mediated electrophysiologic effect^{19,20} nor due to any other direct effect of the drug, but that it is secondary to activation of baroreceptor reflexes. Similar inferences were drawn by Waxman and Wald⁵ in patients with ventricular tachycardia. In their study, the ability of phenylephrine to terminate a sustained arrhythmia was potentiated by edrophonium and reduced by atropine, providing evidence that a reflex cholinergic mechanism and not a direct α -adrenergic action was responsible for the antiarrhythmic effect.

Role of heart rate and of vagal activation: Slowing of heart rate preceded or accompanied VPC suppression in every patient, in agreement with previous anecdotal observations.^{10,11}

The relative antiarrhythmic role of heart rate and of autonomic changes was clarified by the use of atrial pacing. When heart rate was restored to the preinfusion values, VPCs reappeared, but their mean number remained significantly lower than that observed in control conditions. The persistence of a 40% reduction in VPC frequency, despite correction of bradycardia, indicates that the effect of heart rate on ectopic activity, al-

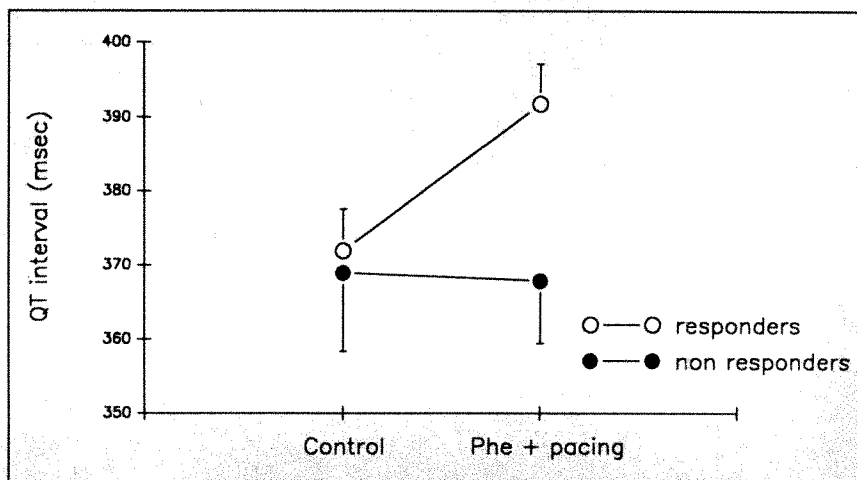
though important, does not fully explain the observed results; this suggests that vagal reflexes might modulate arrhythmogenesis irrespective of changes in heart rate. This effect may be accomplished by modifications of the electrical properties of ventricular tissues, particularly automaticity and refractoriness.²¹

Vagal stimulation can suppress idioventricular automaticity in dogs with complete heart block⁸; a detailed clinical case has been reported showing that vagal activity may modulate idioventricular rhythm.⁶ In our patients, the coupling interval of VPCs remained unchanged during phenylephrine and pacing compared with control conditions, and this argues against the presence of a similar mechanism.

Ventricular refractoriness is prolonged by vagal activation.²²⁻²⁵ Taking circus movement reentry as a model for ventricular ectopy, it is reasonable to speculate that vagal activation could become antiarrhythmic by prolonging refractoriness without changing conduction velocity, thus producing a bidirectional block. This effect is probably magnified during bradycardia, another factor that prolongs refractoriness. These combined effects may act synergistically, leading to a complete suppression of VPCs when heart rate is allowed to decrease during vagal activation. Similar mechanisms could be operative in the VPC suppression reported here and in the prevention of lethal arrhythmias observed among animals and patients with well-preserved baroreflex sensitivity after myocardial infarction.^{26,27}

QT interval: A relatively small but significant prolongation of the QT interval was observed in the responders group, whereas no change was found in the nonresponders. This suggests that prolongation of repolarization takes place only in patients with an adequate baroreceptor response. This effect cannot be ascribed to a direct α -adrenergic action, which could potentially prolong action potential duration²⁰ and repolarization,¹⁹

FIGURE 4. Effect of phenylephrine (Phe) infusion on the QT interval in both the responders (open circles) and the nonresponders (closed circles). Values are expressed as mean \pm standard error.



because a greater amount of phenylephrine was infused in the nonresponders who did not have a prolongation of the QT interval.

The influence of the afterload increase on the duration of repolarization by way of a mechanoelectrical feedback²⁸ is probably irrelevant, because the change in blood pressure was similar in the 2 groups.

The mechanism for QT prolongation involves a reflex vagal activation or a decrease in sympathetic activity, or both. The amount of QT prolongation (20 ms, +5.4%) is greater than the increments observed after β blockade in several studies (7 to 9 ms) when heart rate was maintained constant by pacing.²⁹⁻³¹ This indicates that reflex cholinergic activation prolongs repolarization, as suggested by the effect of atropine on QT duration after pretreatment with propranolol.^{29,30} The entity of QT prolongation is probably explained by the concomitant decrease of sympathetic activity operating in the baroreceptor reflex.¹⁷

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Left Ventricular Shape as a Determinant of Functional Mitral Regurgitation in Patients with Severe Heart Failure Secondary to Either Coronary Artery Disease or Idiopathic Dilated Cardiomyopathy

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The relation between left ventricular (LV) shape and functional mitral regurgitation (MR) was evaluated in 39 patients with congestive heart failure. Heart failure was due to coronary artery disease in 23 patients (group I) and to idiopathic dilated cardiomyopathy in 16 (group II). LV shape was quantitated based on the ratio of LV major-to-minor axis and LV sphericity index calculated at end-systole and end-diastole. In group I, 9 patients had angiographic evidence of MR and 14 did not. In group II, 10 patients had MR and 6 did not. Within each group, there were no differences between patients with and without MR with regard to LV chamber volume and regional segmental wall motion abnormalities. In both groups, however, a significant difference was observed between patients with and without MR with respect to end-systolic and end-diastolic LV shape indexes. In group I, the end-systolic major-to-minor axis ratio was lower in patients with (1.42 ± 0.04) than without (1.72 ± 0.05) MR ($p < 0.001$). Similar differences were observed in group II (1.41 ± 0.06 vs 1.69 ± 0.04) ($p < 0.01$). In group I, the end-systolic sphericity index was also greater in patients with (0.32 ± 0.02) than without (0.25 ± 0.01) MR ($p < 0.02$). Similar differences were observed in group II (0.37 ± 0.03 vs 0.26 ± 0.01) ($p < 0.02$). These data indicate that in patients with severe heart failure, functional MR is present in those who manifest a more spherical LV cavity.

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Mitral regurgitation (MR) often develops in patients with heart failure despite the presence of a normal mitral valve. The mechanisms of this functional MR are not fully understood. Traditionally, MR in patients with heart failure has been attributed to left ventricular (LV) dilatation.¹ LV enlargement, however, can be associated with derangement of many of the integral components of the mitral valve complex,² any one of which can lead to MR. Dilatation of the mitral valve anulus has received some attention as a possible mechanism of functional MR in patients with heart failure.³ Boltwood et al³ demonstrated that patients with dilated cardiomyopathy and auscultatory evidence of MR had a greater increase of mitral anular area than patients without auscultatory evidence of MR. However, other investigators have failed to show a good correlation between the presence of functional MR and dilatation of the mitral anulus.⁴⁻⁶ Papillary muscle dysfunction alone was shown not to lead to MR unless accompanied by injury to the overlying LV wall.⁷⁻⁹ Perloff and Roberts² proposed an alternative mechanism to explain MR in patients with heart failure, which is based on LV shape changes. The present study expands on this concept by examining the relationship between LV shape and functional MR in patients with heart failure due to either coronary artery disease or dilated cardiomyopathy.

METHODS

Patients: In all, 47 patients were studied. All patients underwent cardiac catheterization for ventriculography and coronary arteriography. Sixteen patients had idiopathic dilated cardiomyopathy with angiographically normal coronary arteries, 23 had heart failure due to coronary artery disease, and 8 had normal LV function and coronary arteries, and were used as controls. Of the 23 patients with coronary artery disease, 1 coronary artery was narrowed $>50\%$ in diameter in 1 patient, 2 arteries were narrowed in 7 patients, and 3 arteries were narrowed in 15 patients. Of these 23 patients, 17 had a history of an acute myocardial

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TABLE I Clinical, Hemodynamic and Angiographic Features in Control Subjects, Patients with Coronary Artery Disease (group I) and Patients with Dilated Cardiomyopathy (group II)

	Control	Group I (CAD)	Group II (DC)
No. of patients	8	23	16
Men/women	3/5	18/5	6/10
Heart rate (beats/min)	83 ± 5	91 ± 2	95 ± 4
Mean aortic pressure (mm Hg)	104 ± 4	94 ± 3	97 ± 4
LVED pressure (mm Hg)	14 ± 2	22 ± 2	21 ± 3
LVEF (%)	76 ± 1	24 ± 1	22 ± 1
LVES volume index (ml/m ²)	17 ± 1	85 ± 6	115 ± 12
LVED volume index (ml/m ²)	71 ± 2	112 ± 7	147 ± 15

CAD = coronary artery disease; DC = dilated cardiomyopathy; ED = end-diastolic; EF = ejection fraction; ES = end-systolic; LV = left ventricular.

infarction which had healed and 1 had an acute myocardial infarction 5 days before catheterization. Patients were excluded from the study if they had (1) LV ejection fraction >30%, (2) primary valvular heart disease including mitral valve prolapse, and (3) angiographic evidence of LV aneurysm.

Ventriculography: A left ventriculogram was obtained in all patients in the right anterior oblique projection during the injection of 30 to 45 ml of contrast material (RENO-M-60, Squibb Diagnostics) and was recorded on 35-mm cine at 50 frames/s. Correction for image magnification was made with a calibrated grid placed at the level of the left ventricle. LV chamber volumes at end-systole and end-diastole were calculated using the area-length method.¹⁰ The end-systolic and end-diastolic volume indexes were calculated as the ratio of chamber volume to body surface area. LV ejection fraction was calculated as the ratio of the difference between end-diastolic and end-systolic volume to end-diastolic volume. Premature beats and postextrasystolic beats were excluded from the analysis. The presence and severity of MR was evaluated qualitative-

ly by noting the degree of opacification of the left atrium during ventriculography. A scale of 1+ (mild), 2+ (moderate), 3+ (moderately severe) and 4+ (severe) was used to describe the severity of MR.¹¹

Quantitation of left ventricular shape: Two methods were used to quantitate global LV shape. In the first method, the shape of the left ventricle was quantitated from angiographic silhouettes based on the ratio of the major-to-minor axis calculated at end-systole and end-diastole.¹² As this ratio decreases (approaches unity), the shape of the left ventricle approaches that of a sphere. The second method is an adaptation of the sphericity index described by Lamas et al.¹³ The sphericity index was calculated at end-systole and end-diastole as the volume of the left ventricle divided by the volume of a sphere whose diameter is equal to the major axis of the ventricle. As this ratio increases, the shape of the left ventricle approaches that of a sphere.

Quantitation of regional left ventricular wall function: Segmental function of the LV wall was quantitated in patients with heart failure using the area method.¹⁴ This analysis was performed to determine if LV segmental wall motion abnormalities were present to account for functional MR. The method divides the end-systolic and end-diastolic ventricular silhouettes into 6 regions (anterobasal, anterolateral, anteroapical, posteroapical, diaphragmatic and posterobasal). To define these regions, perpendiculars were drawn from points that divided the major axis of the left ventricle into thirds.¹⁵ All reference systems were applied to the end-systolic and end-diastolic LV silhouettes independently to correct for any motion of the heart in space except rotation.¹⁴ The regional fractional area of shortening was calculated as the difference between the local end-diastolic and end-systolic areas divided by the local end-diastolic area ×100. The persons performing

TABLE II Left Ventricular Ejection Fraction, Chamber Volumes and Shape Indexes in Control Subjects and in Group I and II Patients With and Without Mitral Regurgitation

	Control	Group I (CAD)		Group II (DC)	
		No MR	MR	No MR	MR
No. of patients	8	14	9	6	10
Ejection fraction (%)	76 ± 1	24 ± 1	24 ± 2	23 ± 2	21 ± 2
ES volume index (ml/m ²)	17 ± 1	86 ± 8	85 ± 8	109 ± 24	119 ± 14
ED volume index (ml/m ²)	71 ± 2	112 ± 10	110 ± 10	141 ± 28	151 ± 17
ES axis ratio	2.19 ± 0.04	1.72 ± 0.05	1.42 ± 0.04	1.69 ± 0.04	1.41 ± 0.06
			<0.001		<0.01
ED axis ratio	1.58 ± 0.02	1.63 ± 0.05	1.36 ± 0.05	1.62 ± 0.03	1.38 ± 0.05
			<0.01		<0.01
ES sphericity index	0.14 ± 0.01	0.25 ± 0.01	0.32 ± 0.02	0.26 ± 0.01	0.37 ± 0.03
			<0.02		<0.02
ED sphericity index	0.25 ± 0.01	0.29 ± 0.02	0.37 ± 0.02	0.30 ± 0.01	0.40 ± 0.03
			<0.01		<0.01

Probabilities are based on comparisons within each group (I and II) between no mitral regurgitation and mitral regurgitation.

CAD = coronary artery disease; DC = dilated cardiomyopathy; ED = end-diastolic; ES = end-systolic; MR = mitral regurgitation.

these measurements and measurements of LV shape were not blinded as to the presence or absence of MR in any given patient.

Data analysis: Patients with heart failure were divided into 2 groups. Group I consisted of 23 patients with heart failure due to coronary artery disease. Group II consisted of 16 patients with dilated cardiomyopathy. Each group was divided into 2 subgroups, namely those with and without MR. A third group consisted of 8 control subjects. Comparisons within each group between patients with and without MR were made using Student's paired *t* test. Intergroup comparisons were based on a *t* statistic for 2 means. For both tests, a probability of <0.05 was considered significant. All data are reported as mean \pm standard error of the mean.

RESULTS

None of the patients in the control group had angiographic evidence of MR. Among group I patients, 9 of 23 (39%) had 1+ to 3+ MR. Among group II patients, 10 of 16 (63%) had 1+ to 2+ MR. The clinical, hemodynamic and angiographic features in normal subjects and in group I and II patients are listed in Table I.

Left ventricular shape in patients with coronary artery disease: In patients with coronary artery disease (group I), there was no difference in LV ejection fractions, end-systolic and end-diastolic volume indexes (Table II) or regional wall motion abnormalities (Table III) between those with and without MR. In contrast, a distinct difference was observed between patients with and without MR with respect to shape of the left ventricle. Patients with MR had a more spherical left ventricle than patients without MR. Figure 1 shows the end-systolic and end-diastolic LV angiographic silhouettes in a control subject and in patients with and with-

TABLE III Left Ventricular Regional Fractional Area of Shortening in Group I and II Patients With and Without Mitral Regurgitation

LV Segment	Group I (CAD)		Group II (DC)	
	No MR	MR	No MR	MR
Anterobasal	27 \pm 4	28 \pm 4	16 \pm 2	23 \pm 5
Anterolateral	17 \pm 3	13 \pm 3	16 \pm 2	15 \pm 3
Anteroapical	19 \pm 4	8 \pm 3	22 \pm 4	10 \pm 5
Posteroapical	5 \pm 4	18 \pm 7	13 \pm 11	13 \pm 7
Diaphragmatic	6 \pm 3	13 \pm 3	17 \pm 3	14 \pm 2
Posterobasal	12 \pm 4	15 \pm 3	12 \pm 3	13 \pm 6

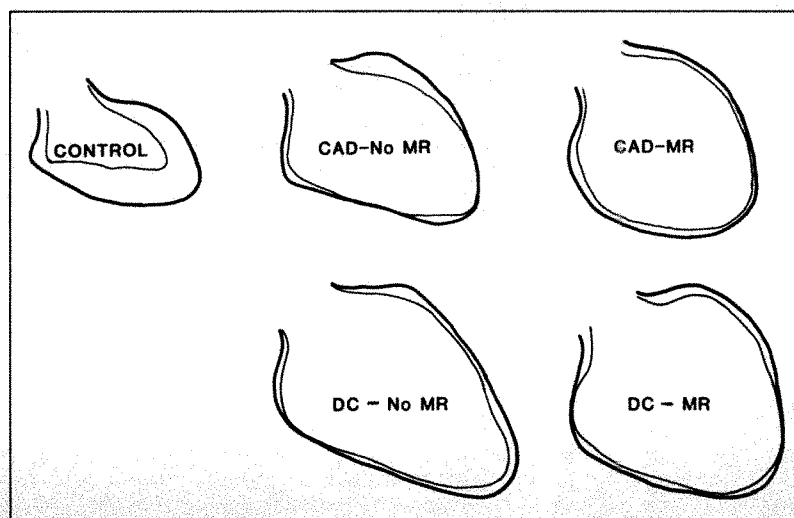
CAD = coronary artery disease; DC = dilated cardiomyopathy; LV = left ventricular; MR = mitral regurgitation.

out MR. In this group, 7 of 9 patients with MR (78%) and 11 of 14 without MR (79%) had a history of acute myocardial infarction.

In group I, the end-systolic major-to-minor axis ratio was significantly lower in patients with (1.42 ± 0.04) than without (1.72 ± 0.05) MR ($p < 0.001$) (Figure 2). The end-diastolic major-to-minor axis ratio was also lower in patients with MR (1.36 ± 0.05 vs 1.63 ± 0.05 ; $p < 0.01$). Concordantly, the end-systolic sphericity index was significantly higher in patients with than without MR (0.32 ± 0.02 vs 0.25 ± 0.01 ; $p < 0.02$) (Figure 2). The end-diastolic sphericity index was also higher in patients with MR (0.37 ± 0.02 vs 0.29 ± 0.02 ; $p < 0.01$).

Left ventricular shape in patients with dilated cardiomyopathy: In group II patients, there was also no difference in LV ejection fraction, end-systolic and end-diastolic volume indexes (Table II) or regional wall motion abnormalities (Table III) between patients with and without MR. A distinct difference, however, was observed between patients with and without MR with respect to shape of the left ventricle. In this cohort of

FIGURE 1. End-systolic (thin line) and end-diastolic (thick line) left ventricular angiographic silhouettes in a control subject (CONTROL), a patient with coronary artery disease (CAD) and no mitral regurgitation (MR) (CAD-No MR), a patient with CAD and MR (CAD-MR), a patient with dilated cardiomyopathy (DC) and no MR (DC-No MR), and a patient with DC and MR (DC-MR). Note the more spherical shape of the left ventricle at both end-systole and end-diastole in patients with MR.



patients, those with MR manifested a more spherical left ventricle than those without MR (Figure 1).

In group II, the end-systolic major-to-minor axis ratio was significantly lower in patients with (1.41 ± 0.06) than without (1.69 ± 0.04) MR ($p < 0.01$) (Figure 3). The end-diastolic major-to-minor axis ratio was also lower in patients with MR (1.38 ± 0.05 vs 1.62 ± 0.03 ; $p < 0.01$). Concordantly, LV sphericity index at end-systole was higher in patients with than without MR (0.37 ± 0.03 vs 0.26 ± 0.01 ; $p < 0.02$) (Figure 3), and at end-diastole it was higher in patients with MR (0.40 ± 0.03 vs 0.30 ± 0.01 ; $p < 0.01$).

DISCUSSION

Heart failure resulting from myocardial infarction with significant loss of viable myocardium or from dilated cardiomyopathy is often associated with transformation of the shape of the LV chamber from that of an ellipsoid to one that more closely approximates a sphere.^{12,16} This shape change of the left ventricle has been shown to be intimately related to its performance.^{12,13,16-18} In patients with dilated cardiomyopathy, a more spherical LV chamber was associated with higher end-systolic wall stress, an abnormal distribution of fiber shortening and a poor long-term survival.^{12,17,18} Patients who developed a more spherical LV chamber a few weeks after acute anterior wall infarction showed significantly lower exercise capacity and a higher propensity to develop heart failure than patients who developed a lesser degree of LV sphericity.¹³ The present study describes yet another undesirable feature of LV shape changes. In patients with heart failure due to ei-

ther coronary artery disease or dilated cardiomyopathy and LV ejection fraction $\leq 30\%$, a more spherical LV chamber was associated with the presence of functional MR. The presence of MR was not related to LV chamber size, nor could it be accounted for by the presence of regional LV wall motion abnormalities.

In heart failure, the presence of functional MR is frequently attributed to 1 of 3 factors: LV enlargement, dilatation of the mitral annulus or dysfunction of the papillary muscles. The results of the present study demonstrate that LV enlargement alone does not account for the presence of MR. The relation between functional MR and mitral annular dilatation was examined by Boltwood et al³ in patients with dilated cardiomyopathy using quantitative echocardiography. They observed a greater increase in the annular area of the mitral valve in patients with auscultatory evidence of MR than in that seen in patients without evidence of MR.³ However, these investigators did not examine differences of LV shape in their patient population and its relation to MR. The importance of annular dilation in the etiology of functional MR in patients with heart failure is not shared by other investigators who also examined this possibility.^{2,4-6} A cross-sectional echocardiographic study by Chandraratna and Aronow,⁶ also in patients with dilated cardiomyopathy, showed that mitral annular dilatation can in fact occur in these patients but that it did not correlate with the presence of functional MR. Bulkley and Roberts⁵ suggested that dilatation of the mitral annulus is a rare cause of functional MR. Autopsy data indicate that the mitral valve leaflets have a surface area that is nearly twice that of the annular

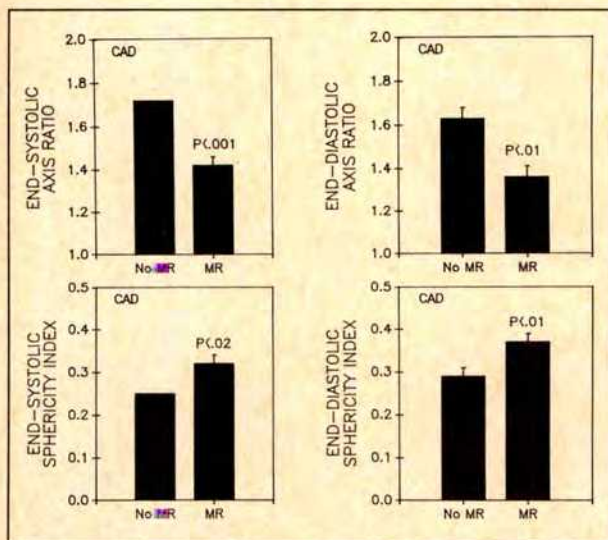


FIGURE 2. Top, bar graphs (mean \pm standard error of the mean) depicting left ventricular end-systolic (left) and end-diastolic (right) major-to-minor axis ratios in patients with coronary artery disease (CAD) with and without mitral regurgitation (MR). Bottom, bar graphs depicting left ventricular end-systolic (left) and end-diastolic (right) sphericity indexes in the same group of patients with CAD.

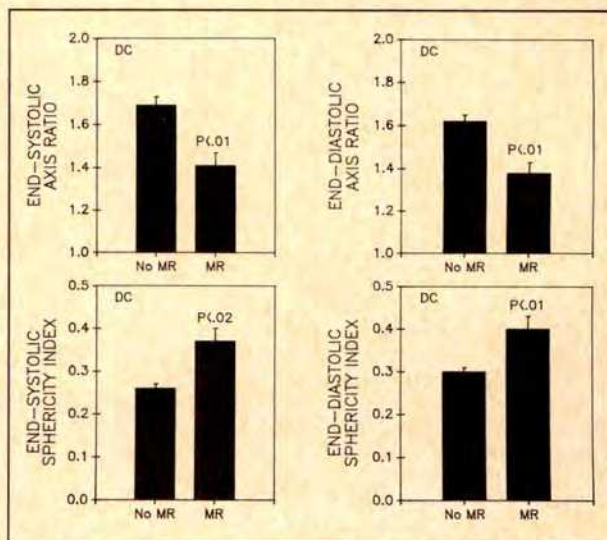


FIGURE 3. Top, bar graphs (mean \pm standard error of the mean) depicting left ventricular end-diastolic (left) and end-systolic (right) major-to-minor axis ratios in patients with dilated cardiomyopathy (DC) with or without mitral regurgitation (MR). Bottom, bar graphs depicting left ventricular end-systolic (left) and end-diastolic (right) sphericity indexes in the same group of patients with DC.

area.¹⁹ On this basis, considerable anular dilatation would be required to prevent leaflet coaptation. In the present study, we did not address the possibility of mitral anular dilatation as a mechanism of functional MR because of inherent angiographic limitations for such measurements. Obviously, our data do not exclude the possibility that mitral anular dilatation can contribute to the development of MR in patients with heart failure. However, these data provide compelling evidence that changes of LV shape (increased LV sphericity) is an important factor that must be considered in the etiology of functional MR in patients with heart failure.

Clinical acceptance of an association between papillary muscle dysfunction and functional MR is widespread despite the lack of objective support. Studies in patients and in laboratory animals have shown that papillary muscle infarction alone, without injury to the overlying LV wall, may not result in MR.^{2,7,8} Godley et al⁹ examined the association between papillary muscle dysfunction and MR in patients with prior myocardial infarction and recent clinical evidence of papillary muscle dysfunction. Of 24 patients with echocardiographic evidence of incomplete closure of the mitral valve, 23 showed dyskinesia of the LV wall in the region immediately surrounding 1 of the papillary muscles.⁹ In the present study, we did not observe significant differences in LV segmental wall motion abnormalities among patients with and without MR, which could account for the presence of functional MR.

The mechanism by which alterations of LV shape can lead to MR is not clear, nor was an attempt made in the present study to elucidate such a mechanism. The explanations offered in reports by Perloff and Roberts^{2,4} merit consideration. In the normally ellipsoidal-shaped LV chamber, the position of the papillary muscles permits their contraction to exert a vertical force on the chordae tendineae. Application of this force moves the mitral valve leaflets together during isovolumic contraction and restrains their motion during LV ejection.^{2,4} In a more spherically shaped ventricle, the papillary muscles undergo lateral migration and are no longer vertically aligned with the mitral annulus. In this situation, the forces exerted on the leaflets through the

chordae tendineae become more lateral rather than vertical. This lateral tension may act to prevent apposition of the leaflets and renders the valve incompetent.^{2,4}

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Effects of Enoximone on Exercise Tolerance in Patients with Mild to Moderate Heart Failure

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To evaluate the efficacy of enoximone on exercise tolerance in patients with mild to moderate heart failure, 33 patients underwent cardiopulmonary exercise tests before and 3 hours after placebo or after receiving 25 or 100 mg of enoximone administered randomly in a double-blind manner. The electrocardiogram was monitored and blood pressure measured every minute throughout cycle ergometer exercise testing with a ramp protocol in which the work rate increased 1 W every 6 seconds after a 4-minute 20-W warm-up. Minute ventilation, oxygen uptake (VO_2), and carbon dioxide output were measured every 10 seconds in order to determine anaerobic threshold (AT) and peak VO_2 . Five patients were excluded from evaluation before breaking the double-blind key because of insufficient data. Heart rate increased and systolic blood pressure decreased throughout the testing only in the group taking 100 mg ($n = 10$). Significant increases in AT (14.4 to 16.2 ml/min/kg) and peak VO_2 (20.8 to 22.9 ml/min/kg) were observed in the group taking 100 mg. The increases in AT showed a dose response, namely +0.7% in the placebo ($n = 9$), +6.9% in the 25-mg ($n = 9$) and 12.5% in the 100-mg group. The work rates at the AT point increased in the 25- and 100-mg groups. These results indicate that a single oral administration of enoximone improves exercise tolerance in patients with mild to moderate heart failure.

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The acute effects of phosphodiesterase inhibitors such as enoximone, amrinone and milrinone on severe congestive heart failure are well-known¹⁻³ and include improvement of hemodynamics and exercise capacity.⁴ It is still unclear whether these drugs are beneficial for patients with milder heart failure. One of the main goals of treatment for chronic heart failure without severe congestion is to improve exercise capacity, with a consequent improvement in daily activity. There have been few well-controlled studies of the acute effects of enoximone on exercise capacity in patients with mild to moderate heart failure. We conducted this study to evaluate the acute effects of oral enoximone on exercise capacity by measuring anaerobic threshold (AT) in patients with mild to moderate heart failure.

METHODS

Patients: Thirty-three patients (22 men and 11 women, mean age \pm standard deviation 61 ± 8 years [range 48 to 75]) with chronic heart failure were enrolled in the study. No patient had severe congestion on chest x-ray or physical examination. Thirty-one patients were in New York Heart Association functional class II and 2 were in class III. The underlying diseases were regurgitant valvular heart disease in 12 patients, ischemic heart disease in 12, hypertensive heart disease in 5, dilated cardiomyopathy in 2, and other diseases in 2. Patients with stenotic valvular heart disease, hypertrophic obstructive cardiomyopathy, possible episode of angina pectoris, severe arrhythmias and anemia were excluded.

Protocol: The patients were randomly allocated in a double-blind manner into 3 treatment groups: placebo, and 25 and 100 mg of enoximone. Cardiopulmonary exercise tests were performed before and 3 hours after administering the drug. All vasodilators and inotropes were withdrawn at least 1 week before exercise testing with the exception of digitalis and diuretic drugs, which were given after the second exercise test on the test day.

Method of exercise testing: We used the ramp-loading technique for the cardiopulmonary exercise test with an electromagnetically controlled cycle ergometer (Siemens-Elema 930B with ramp slope controller). The work rate was increased 1 W every 6 seconds from a 4-minute 20-W, 60 rpm warming-up stage up to the

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point of patient exhaustion. The patient was monitored throughout by a 12-lead electrocardiogram (Stress Test System ML-8000, Fukuda Denshi, Tokyo, Japan), and cuff blood pressure was measured every minute (Stress Test Blood Pressure Monitor STPD-680F, Collin Denshi, Aichi, Japan). At the same time, expired gas analysis was performed throughout the exercise using an Aerobics Processor 391 (Nihon Denki San-ei, Tokyo, Japan). The system was carefully calibrated before each study, and oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}E$) were measured every 10 seconds. The ventilatory equivalent for O_2 ($\dot{V}E/\dot{V}O_2$), CO_2 ($\dot{V}E/\dot{V}CO_2$) and gas exchange

ratio (R ; $\dot{V}CO_2/\dot{V}O_2$) were computed simultaneously and displayed with $\dot{V}O_2$ on a monitor during measurement using personal computer (NEC PC-9801, Foxboro, Massachusetts) with software developed in our laboratory.

Determination of anaerobic threshold: The AT point was determined visually by 4 experienced reviewers before opening the key code of randomization. The criteria used for determination of AT were^{5,6}: (1) The $\dot{V}E/\dot{V}O_2$ curve, which was either flat or decreasing, begins to rise as the $\dot{V}E/\dot{V}CO_2$ curve remains constant or decreases. (2) Gas exchange ratio, which was flat or gently rising, changes to a steeper slope. To determine

TABLE I Background of Patients and Exercise Parameters Before and After Therapy in Each Group*

Pt. No.	Age (yr) & Sex	Weight (kg)	Height (cm)	Cause of Diseases	NYHA	AT				Peak Exercise				Blood Concentration	
						VO ₂		WR		VO ₂		WR		Enoximone MDL-19,438	
						Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Placebo															
2	61 F	49	151	ASR/MSR	II	18.0	19.3	53	51	21.6	26.5	73	80	0	0
6	64 F	51	148	MS/AR	II	12.1	10.4	38	40	20.0	17.6	78	80	0	0
8	59 F	53	148	IHD	II	14.2	14.0	51	50	21.7	20.4	84	82	0	0
11	57 M	58	158	MR	II	14.2	16.4	50	63	27.8	26.9	134	133	0	0
14	65 M	65	161	HHD	II	14.4	14.1	56	65	31.2	26.9	141	135	0	0
19	63 M	62	164	MR	III	13.3	14.9	63	68	18.4	17.7	99	96	0	0
21	56 M	57.5	165	DCM	II	18.6	16.8	60	60	26.7	23.0	105	93	0	0
25	62 F	45	140	MSR	II	17.9	19.1	56	65	24.8	21.0	82	85	0	0
31	63 F	49	151	OMI	II	11.9	10.7	46	41	14.8	14.0	58	58	0	0
Mean	61.1	55.1	154			15.0	15.1	52.6	55.9	23.0	21.6	94.9	93.6	0	0
±SD	±3.1	±6.8	±8.5			±2.6	±3.2	±7.5	±10.7	±5.1	±4.6	±27.8	±25.3	±0	±0
p Value						p = 0.80		p = 0.14		p = 0.16		p = 0.49			
25 mg															
5	59 F	42	144	MSR	II	9.2	7.9	30	38	13.6	11.9	53	60	32	18
9	58 M	65	165	OMI	II	12.5	12.4	45	56	19.7	22.8	98	96	32	229
12	63 F	46.5	144	OMI	II	13.7	16.0	36	48	20.6	24.3	82	84	32	228
13	66 M	52.5	165	AR	II	17.8	17.6	58	70	25.9	24.2	110	112	24	341
16	65 M	73	159	OMI	II	11.9	13.4	58	63	20.3	21.6	127	123	26	191
24	75 M	51	147	OMI	II	14.7	15.5	50	46	22.6	21.5	80	79	48	323
26	63 M	56	166	MS/AR	II	12.9	14.0	53	58	19.0	18.2	88	90	112	280
28	63 F	51	147	HHD	II	12.2	11.9	45	41	19.7	19.8	77	76	82	657
32	59 M	66	171	MSR/AR	II	12.5	16.0	76	81	19.5	23.7	123	129	35	194
Mean	63.4	55.9	156.4			13.0	13.9	50.1	55.7	20.1	20.9	93.1	94.3	47	273
±SD	±5.2	±10.1	±10.9			±2.3	±2.9	±13.5	±14.1	±3.2	±3.9	±23.8	±23	±30	±172
p Value						p = 0.13		p = 0.027		p = 0.35		p = 0.34			
100 mg															
1	64 M	65	154	IHD	II	13.1	12.5	60	58	18.6	19.5	102	106	155	897
3	58 M	60	176	IHD	II	16.4	17.5	65	70	28.0	26.7	125	123	541	752
10	64 M	67	170	OMI	II	13.5	14.1	60	70	19.3	19.6	108	112	478	1,463
15	62 M	74	168	HHD	II	12.5	14.0	61	70	19.6	22.3	123	132	133	650
17	48 M	50	162	MR	II	14.2	17.0	43	53	17.6	25.4	80	91	168	111
22	64 F	54	153	OMI	II	20.3	22.1	60	68	23.1	24.4	86	87	278	793
23	61 M	58	155	HHD	II	16.8	21.6	55	56	27.4	27.4	106	94	87	491
27	34 M	65	164	MS/AR	II	14.3	16.7	65	75	20.3	24.1	138	127	207	761
29	54 M	61	156	OMI	II	12.7	12.9	56	59	17.8	21.4	90	102	210	705
33	55 F	47.5	159	MSR/TR	II	10.3	13.2	40	43	15.8	17.7	53	61	366	1,194
Mean	56.4	60.2	161.7			14.4	16.2	56.5	62.2	20.8	22.9	101.1	103.5	262	782
±SD	±9.5	±8.1	±7.7			±2.8	±3.5	±8.6	±10.0	±4.1	±3.3	±24.9	±21.5	±152	±366
p Value						p = 0.0058		p = 0.0024		p = 0.029		p = 0.40			
*There was no significant difference in the age and cardiothoracic ratio (U test), and the characteristics of the patients (chi-square test) among these 3 groups. To compare data before and after the drug, Student's paired t test was used. Patients 4, 7, 18, 20 and 30 were excluded before opening the key code because of insufficient data or protocol violation. AR = aortic regurgitation; ASR = aortic stenosis and regurgitation; AT = anaerobic threshold; DCM = dilated cardiomyopathy; HHD = hypertensive heart disease; IHD = ischemic heart disease; MR = mitral regurgitation; MS = mitral stenosis; MSR = mitral stenosis and regurgitation; NYHA = New York Heart Association functional classification; OMI = old myocardial infarction; SD = standard deviation; TR = tricuspid regurgitation; VO ₂ = oxygen uptake (ml/min/kg); WR = work rate (W).															

*There was no significant difference in the age and cardiothoracic ratio (U test), and the characteristics of the patients (chi-square test) among these 3 groups. To compare data before and after the drug, Student's paired *t* test was used. Patients 4, 7, 18, 20 and 30 were excluded before opening the key code because of insufficient data or protocol violation. AR = aortic regurgitation; ASR = aortic stenosis and regurgitation; AT = anaerobic threshold; DCM = dilated cardiomyopathy; HHD = hypertensive heart disease; IHD = ischemic heart disease; MR = mitral regurgitation; MS = mitral stenosis; MSR = mitral stenosis and regurgitation; NYHA = New York Heart Association functional classification; OMI = old myocardial infarction; SD = standard deviation; TR = tricuspid regurgitation; $\dot{V}O_2$ = oxygen uptake (ml/min/kg); WR = work rate (W).

$\dot{V}O_2$ at AT point, measured $\dot{V}O_2$ was fitted to a linear regression line and the value corresponding to AT was taken as $\dot{V}C_{50}$ at AT value. Peak $\dot{V}O_2$ was defined as the average $\dot{V}O_2$ of the last 30 seconds of exercise.

Blood concentration of the drug: The blood sample was obtained 3 hours after administration of the drug in order to measure enoximone and its active metabolite, MDL-19,438, concentration.

Statistical analysis: Statistical analysis was performed using the Student paired *t* test to compare baseline and measurements after drug administration, the chi-square test to compare patient characteristics in each group, and the U test for patients' background data. Statistical significance was at $p < 0.05$ (2-tailed). Results are expressed as mean \pm standard deviation.

RESULTS

Five patients were excluded from evaluation before opening key codes because of insufficient data. Evaluations were made in the remaining 28 patients, 9 in the placebo group, and 9 in the 25-mg and 10 in the 100-mg group. There was no significant difference in patients' background among these groups (Table I).

Average heart rate did not change in the placebo and 25-mg groups throughout the exercise test. But in the 100-mg group, the average heart rate increased significantly from 72 to 85 beats/min at rest, from 88 to 96 at 20-W warm-up and from 149 to 163 at peak exercise. Blood pressure showed no significant change in the placebo and 25-mg groups; however, in the 100-mg group, enoximone decreased systolic blood pressure

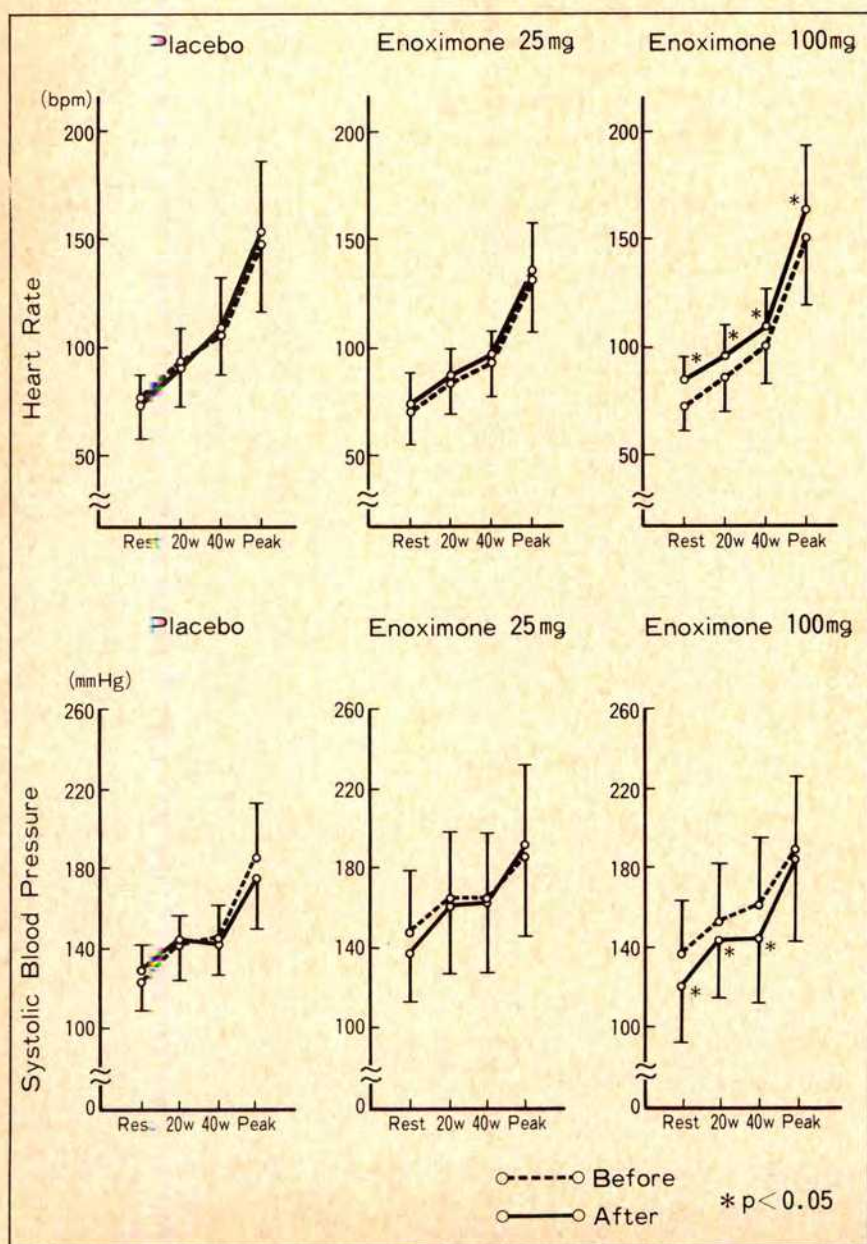


FIGURE 1. Changes in heart rate (upper panel) and systolic blood pressure (lower panel) before and after administration of each drug. In the group taking 100 mg of enoximone, heart rate increased and systolic blood pressure decreased during exercise testing.

by an average of 17 mm Hg at rest, 9 mm Hg at warm-up and 17 mm Hg at 40 W (Figure 1).

The values of AT and peak $\dot{V}O_2$ before and after administration are listed in Table I. No change was seen in AT in the placebo group. In the 25-mg group, AT increased from 13.0 to 13.9 ml/min/kg, not significant statistically ($p = 0.13$). A significant increase in AT was observed in the 100-mg group, from 14.4 to 16.2 ml/min/kg ($p = 0.0058$). The increase of ATs showed dose response (chi-square = 0.066, Scheffe-type multiple comparison test), namely +0.7% in the placebo, +6.9% in the 25-mg and 12.5% in the 100-mg groups. Peak $\dot{V}O_2$ was similar to AT. Only 100 mg of enoximone improved peak $\dot{V}O_2$ significantly, from 20.8 to 22.9 ml/min/kg ($p = 0.029$).

The work rates at AT increased significantly in the 25- and 100-mg groups, but not in the placebo group. The work rate at peak exercise remained unchanged in all groups (Table I).

The ratio of increase in $\dot{V}O_2$ to increase in work rate ($\Delta\dot{V}O_2/\Delta WR$) was determined by linear regression of $\dot{V}O_2$ plots from 1 minute after the start of ramping up to the approximate midpoint between AT and peak exercise. This ratio index reflects adequacy of oxygen delivery to the working muscle. There was a rough relation between percent change in AT and percent change in $\Delta\dot{V}O_2/\Delta WR$ (Figure 2).

The blood levels of enoximone and its active metabolite, MDL-19,438, are also demonstrated in Table I. MDL-19,438 has one-sixth the potency of enoximone. There was no apparent relation between the degree of improvement in exercise capacity and plasma concentrations of enoximone and its metabolite.

DISCUSSION

The goals of treatment for patients with heart failure include improvement of their quality of life and prolongation of life. To achieve the former, improvement in exercise tolerance — and, by implication, evaluation of drugs for heart failure by exercise testing — is particularly important in patients with mild to moderate heart disease as seen in this study. Because the indexes of cardiac function at rest do not adequately represent functional capacity during exercise,⁷ assessment of capacity by exercise testing has gained increasing acceptance in the evaluation of treatment.

In 1964, Wasserman and McIlroy⁸ established the methodology for evaluating exercise capacity using AT in patients with heart disease. AT is an objective index that can be obtained safely from submaximal exercise testing, unlike maximal $\dot{V}O_2$. Recently, we confirmed the basic validity of AT determined by respiratory gas exchange measurements⁹ in agreement with other in-

vestigators.^{10,11} Moreover, AT primarily depends on oxygen delivery to working muscle. This links it to the pathophysiology of heart failure.

There has been only 1 report, to our knowledge, that evaluated the acute effects of a phosphodiesterase inhibitor on exercise capacity and AT. White et al⁴ reported that intravenous infusion of milrinone improved AT acutely. But they enrolled only patients who had a hemodynamic response to milrinone infusion, and each patient's effective dose was decided in advance of the exercise study. Our study is the first to prove the acute effects of a phosphodiesterase inhibitor on AT in mild to moderate heart failure patients with heterogeneous heart disease without any entry biases.

The reason for the increase in AT is not entirely clear. The increase in AT with long-term treatment with milrinone was reported by Ribeiro et al.¹² They suggested that the increased availability of oxygen to the exercising muscle due to direct vasodilation or withdrawal of sympathetic tone or increasing skeletal muscle oxidative capacity, or both, may be involved. In this study, it is improbable that there was an improvement in metabolic or oxidative capacity in the exercising muscle itself, such as an increase in number of mitochondria, because AT improved within 3 hours of a single oral administration of enoximone. Enoximone has 2 pharmacologic components, inotropism and vasodilation. The failure of an arteriodilator like hydralazine to increase exercise capacity¹³ may be due to the blood flow redistribution to nonexerting organs or decreased perfusion pressure to the working muscle, or both, even though cardiac output increased. Because patients in this study were mostly in New York Heart Association functional class II, their preload should not have been extremely high, and any venodilating action

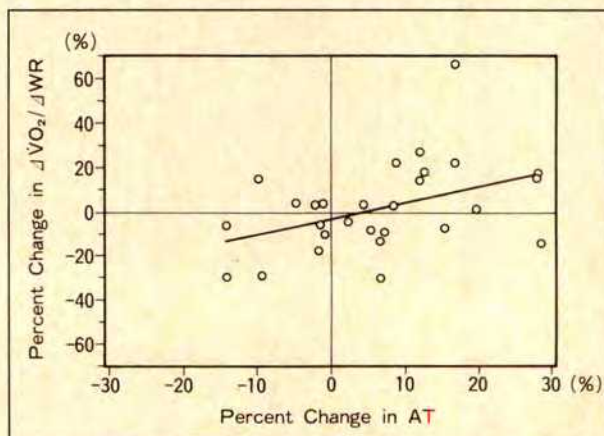


FIGURE 2. Relation between the percent changes of anaerobic threshold (AT) and the ratio of increase in oxygen uptake to increase in work rate ($\Delta\dot{V}O_2/\Delta WR$). There was a rough relation between these 2 parameters ($y = 0.73x - 2.81$, $r = 0.42$, $p = 0.024$).

probably would not improve cardiac performance or output. Recently, we found that the AT point is closely related to the work rate above which the deterioration of left ventricular function occurs during incremental exercise.¹⁴ There was a tendency for $\Delta\dot{V}O_2/\Delta WR$ to increase in patients whose ATs improved (Figure 2). This index represents the degree of aerobic contribution to the working muscle and has been reported to be reduced in many patients with cardiovascular disease.^{9,15} When oxygen delivery cannot meet the demand for increasing work rate, $\Delta\dot{V}O_2/\Delta WR$ becomes smaller. The improvement in $\Delta\dot{V}O_2/\Delta WR$ with increasing AT by a single oral enoximone capsule suggests that its inotropic action is benefiting the patient. Also, the increase in AT in this case was caused mainly by circulating improvement, with minimal improvement in peripheral oxygen use such as that gained through physical exercise. Therefore, the rate of increase in AT expressed by $\dot{V}O_2$ can be considered significant.

There have been reports that showed that enoximone improved the acute hemodynamics but did not produce sustained benefit and was associated with a high mortality.¹⁶ However, the doses used in those studies were high (1.7 to 19 mg/kg 3 or 4 times daily¹⁶). In our study, even 25 mg of enoximone increased the work rate at the AT point, which suggests that there might be sufficient therapeutic effect even with such a low dose without adverse effects.

With regard to the optimal therapeutic dose of enoximone, the results of the long-term effects of low-dose enoximone on exercise capacity, with a well-controlled study design, are needed to address this question.

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Outcome of Infants and Children with Dilated Cardiomyopathy

Alan B. Lewis, MD, and Michelle Chabot, BS

A review of 81 infants and children with dilated, poorly contracting left ventricles without associated structural abnormalities was undertaken to identify risk factors for poor outcome, which could be used in selecting candidates for cardiac transplantation. Significant atrial or ventricular dysrhythmias, or both, were detected on presentation or during follow-up in 24 patients. Arrhythmias were present in only 8 of 51 survivors (16%) but were detected in 16 of 30 patients (53%) who died ($p < 0.05$). Patients dying suddenly were even more likely to have had documented dysrhythmias (8 of 11, $p < 0.05$). Left ventricular shortening fraction was similar in survivors and nonsurvivors ($14.9 \pm 1.0\%$ vs $15.3 \pm 1.7\%$). Left ventricular end-diastolic pressure in 44 patients who had cardiac catheterization averaged 20.8 ± 1.6 mm Hg. Left ventricular end-diastolic pressure was significantly higher in patients who died than in those who survived (29.5 ± 2.2 vs 15.0 ± 1.6 mm Hg, $p < 0.001$). Analysis of actuarial survival revealed that mortality was highest during the first 6 months after presentation (19% mortality). Survival declined more gradually thereafter and was 70% at 2 years, 64% at 5 years and 52% after 11.5 years. Age at initial presentation did not have any significant impact on survival. However, left ventricular end-diastolic pressure > 25 torr was associated with a significantly increased mortality rate ($p < 0.05$). Early cardiac transplantation should be considered in patients with markedly elevated left ventricular end-diastolic pressure or complex atrial or ventricular arrhythmias.

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Dilated cardiomyopathy is a generic description of cardiac muscle disease characterized by a dilated and poorly contracting left ventricle.^{1,2} The clinical features and natural history have been well described in adults in whom the 1-year survival ranges from 65 to 70% and the 5-year survival declines to approximately 50%.³⁻⁵ Severity of left ventricular dysfunction, as measured by left ventricular end-diastolic pressure, has been reported to be a significant prognostic indicator.³ In contrast, recent reports of infants and children with dilated cardiomyopathy have suggested that older age at onset is associated with higher mortality, but these reports found no relation between echocardiographic or hemodynamic indexes of left ventricular performance and survival.^{6,7} This report examines the clinical and laboratory features of children with dilated cardiomyopathy in order to identify patients who should be referred for cardiac transplantation.

METHODS

Patient selection: The medical records of Childrens Hospital of Los Angeles were reviewed from January 1975 to June 1990 to identify patients presenting with a dilated, poorly functioning left ventricle in the absence of congenital or acquired structural cardiac abnormalities. Patients with known metabolic, toxic, collagen-vascular and neuromuscular causes of myocardial dysfunction and patients with clinical or laboratory features consistent with acute myocarditis (positive viral cultures, characteristic increase in convalescent viral antibody titers or histologic evidence of myocarditis⁸ obtained by endomyocardial biopsy or necropsy examination) were excluded. The date of initial presentation was defined as the first documentation of left ventricular dysfunction rather than onset of symptoms since the latter was often vague. Family history, symptoms, treatment and clinical course were assessed. Laboratory studies included chest radiographs, electrocardiograms, echocardiograms, cardiac catheterization and endomyocardial biopsy data and serum carnitine concentrations. Follow-up information was obtained from the outpatient records or from letters sent to the patients' parents and personal physician. Patients who were alive at their last follow-up were listed as survivors.

Statistical analysis: Descriptive statistics are expressed as mean \pm standard error. Survival was esti-

TABLE I Rhythm Abnormalities in Patients with Dilated Cardiomyopathy

Patient Status	SR	Arrhythmias			Total
		Atrial	Ventricular	Both	
All patients	57	4	16	4	81
Alive	43	3	4	1	51
Dead	14	1	12	3	30
Heart failure	11	0	6	2	19
Sudden death	3	1	6	1	11

p < 0.05 arrhythmias in patients dying suddenly versus those with heart failure.
SR = sinus rhythm.

ated by life-table analysis using the variable interval (Kaplan-Meier) method.⁹ Comparison of survival curves was performed using the method of Greenwood¹⁰ for calculating the standard error of interval survival. Clinical and laboratory data were analyzed by unpaired Student's *t* test, multiple linear regression for continuous variables, and chi-square and Fisher's test for discrete variables. A *p* value < 0.05 was considered significant.

RESULTS

Patient profile: In all, 81 patients (41 male and 40 female patients; mean age \pm standard deviation at initial presentation, 3.6 ± 0.6 years; range 1 day to 19.9 years) presenting with congestive heart failure were identified as having dilated cardiomyopathy. The mean age at presentation was not significantly different in survivors compared with nonsurvivors (3.3 ± 1.0 vs 4.5 ± 1.3 , *p* = 0.46). A family history of cardiomyopathy was confirmed in 11 patients, 7 of whom were boys, and was suspected in an additional 9 patients.

Laboratory profile: Electrocardiography demonstrated left ventricular hypertrophy and ST or T-wave changes, or both, in 54 patients. Dysrhythmias (Table I) were detected on presentation or during follow-up in 24 patients and included atrial flutter/fibrilla-

tion (*n* = 4), supraventricular reentrant tachycardia (*n* = 4), frequent (Lown grade 2 to 4A) premature ventricular contractions (*n* = 14), nonsustained ventricular tachycardia (*n* = 1) and ventricular fibrillation (*n* = 5). Four patients had documentation of both atrial and ventricular arrhythmias. Rhythm abnormalities were present in only 8 of 51 survivors (16%). In contrast, dysrhythmias were detected in 16 of 30 patients (53%) who died (*p* < 0.05). Patients who died suddenly were even more likely to have had documented rhythm disturbances (8 of 11, 73%), whereas congestive heart failure was the predominant cause of death in patients without known dysrhythmias (*p* < 0.05). Left ventricular end-diastolic pressure was not significantly different in patients with or without rhythm disturbances (22.2 ± 2.6 vs 20.7 ± 2.0 torr, *p* = 0.69).

The echocardiographically derived left ventricular shortening fraction on presentation was $14.9 \pm 0.9\%$ and increased to $22.4 \pm 1.7\%$ at the last follow-up evaluation. The initial shortening fraction was similar in survivors and nonsurvivors ($14.9 \pm 1.0\%$ vs $15.3 \pm 1.7\%$). There was a tendency for shortening fraction to improve in patients who survived compared with those who died (26.7 ± 1.7 vs 19.6 ± 4.6) but the difference was not statistically significant (*p* = 0.17). Left atrial or left ventricular mural thrombi were detected in 3 patients.

Left ventricular end-diastolic pressure was measured in 44 patients and averaged 20.8 ± 1.6 mm Hg. Patients who died had a significantly higher end-diastolic pressure (Figure 1) compared with those who survived (29.5 ± 2.2 vs 15.0 ± 1.6 mm Hg, *p* < 0.001). Left ventricular end-diastolic pressure was >25 torr in 16 patients; 11 subsequently died, 2 underwent cardiac transplantation and 2 are currently alive, 1 of whom is awaiting transplantation and 1 patient was lost to follow-up. Age at onset was weakly related to left ventricular end-diastolic pressure using multiple regression



FIGURE 1. Left ventricular end-diastolic pressure (LVEDP) was measured in 44 patients at the time of cardiac catheterization or endomyocardial biopsy. Left ventricular end-diastolic pressure was significantly higher in patients who died (*p* < 0.001). Patients who were lost to follow-up or underwent cardiac transplantation are not shown. Means \pm standard error are indicated.

analysis ($r = 0.41$, $p < 0.05$). No other significant association was noted between end-diastolic pressure and other clinical variables including shortening fraction ($r = -0.18$) and dysrhythmias ($p = 0.65$). However, as expected, an elevated end-diastolic pressure was directly related to an increased pulmonary artery pressure ($r = 0.79$) and inversely correlated with cardiac output ($r = -0.60$).

Endomyocardial biopsies were performed in 28 patients. Histopathologic findings included myofiber hypertrophy, necrosis and disarray, interstitial and endocardial fibrosis, vacuolization and "T" tubular, mitochondrial and endoplasmic reticulum abnormalities.

Serum carnitine concentrations were measured in 16 patients and were low in 2. One child was treated with oral carnitine supplementation without significant improvement in left ventricular function. The other patient was an infant who died <2 weeks after presentation before the serum carnitine level was known.

Therapy: All patients were treated with digoxin and 94% received furosemide. Angiotensin-converting enzyme inhibitors (captopril, enalapril) were administered to 33% of patients including most patients presenting in recent years. Intravenous inotropic agents (dobutamine, dopamine, amrinone) were administered on ≥ 1 occasion in 52%. Three patients were treated with antiarrhythmic medications (lidocaine or quinidine, or both). Anticoagulation with warfarin was prescribed in 15 patients.

Follow-up and survival: Mean duration of follow-up for all patients was 3.5 ± 0.5 years (range 0 to 15.5). Fifty-one patients were alive at the time of their last follow-up. Recent updated information could not be obtained in 14 of these patients and therefore they were considered lost to follow-up. Four patients underwent heart transplantation and remain alive. For the purpose of calculation of actuarial survival curves, their clinical data were included until they were withdrawn alive at the time of their last known evaluation or transplantation.¹¹

Twenty-four of the 47 surviving patients (who did not undergo transplantation) were reported to be improved at their last follow-up, i.e., either off all cardiac medications or asymptomatic with medication. Twenty-one patients receiving cardiac medications were alive and stable without overt clinical evidence of congestive heart failure but with mild to moderate exercise intolerance. Finally, 2 patients were reported to have chronic congestive heart failure despite medical therapy, 1 of whom is awaiting transplantation.

Thirty patients died (37%) at a mean of 1.8 ± 0.7 years after onset. Mortality was highest during the first 6 months of presentation (Figure 2). Eight patients died within 1 month (10% mortality) and 15 patients died during the first 6 months (19% mortality). Sur-

vival decreased more gradually thereafter and was 70% 2 years after onset, 64% at 5 years and 52% after 11.5 years. The apparent large decrease in survival rate beyond 11 years is the result of relatively few patients followed and represents only a single death at 11.5 and 13.6 years, respectively. Survival was analyzed further by the patient's age at the time of presentation (Figure 3). Group 1 consisted of 53 patients who presented at age <2 years (mean survival 3.7 ± 0.6) and group 2 consisted of 28 patients who were aged >2 years (mean survival 3.3 ± 0.9). The Kaplan-Meier survival curves for the 2 groups were similar throughout the follow-up period. The divergence noted after 11.5 years is exaggerated by the small number of patients in each group but the difference in cumulative survival is not significant ($p = 0.77$).

Actuarial survival for patients in whom left ventricular end diastolic pressure <25 torr was compared with that in patients with left ventricular end-diastolic pressure >25 torr (Figure 4). Cumulative survival rates were significantly lower in patients with markedly elevated left ventricular end-diastolic pressure over the first 5 years of follow-up ($p < 0.05$). Thereafter, no significant differences were noted, but only 3 patients who had cardiac catheterization were followed >11 years.

DISCUSSION

The outcome for infants and children with dilated cardiomyopathy has been variable in previous reports. Greenwood et al¹² reported a 50% cumulative survival at 15 years in a large group of children with "primary myocardial disease" followed for a mean of 3.4 years. However, they included heterogeneous diagnoses such

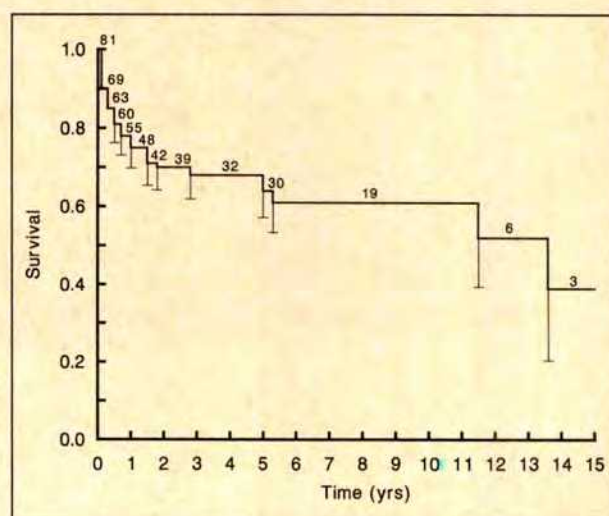


FIGURE 2. Actuarial survival in 81 patients with dilated cardiomyopathy. The highest mortality occurs within the first 6 months of presentation with a somewhat slower decline in the cumulative survival rate over the next 1.5 years. Beyond 2 years, survival decreases slowly but progressively. The number of patients remaining alive during the interval are indicated. The standard error of the cumulative survival is indicated.

as myocarditis, nonobstructive hypertrophic cardiomyopathy and endocardial fibroelastosis. Talierto et al⁶ reported a much smaller group of 24 patients with idiopathic dilated cardiomyopathy who were followed for a mean of 2.5 years. Survival at 2 years was only 50% and declined further to 34% by 5 years. However, only 4 patients were included at the 5-year follow-up interval. Although their analysis suggested that survival may be worse in older children, the difference was not statistically significant. Recently, Griffin et al⁷ reported that children aged >2 years at presentation had a particularly high mortality with <20% survival 2 years after onset. In addition to age at onset, other risk factors for poor outcome included persistent cardiomegaly and ventricular arrhythmias. These observations, if confirmed, have important clinical implications, namely that children with dilated cardiomyopathy presenting at age >2 years should be considered for early cardiac

transplantation. However, as in the report from the Mayo Clinic,⁶ the number of patients included in their series was relatively small. In all, there were 32 patients but only 12 children aged >2 years at onset.

The current series of 81 infants and children appears to be the largest recent report of pediatric patients with dilated cardiomyopathy. The mean duration of follow-up was 3.5 years, with 32 patients alive at 5 years and 20 patients surviving between 6 and 11 years. Age at the time of presentation did not appear to be a significant predictor of outcome. Survival decreased most rapidly during the first 6 months in both age groups and continued to decline progressively over the next 1.5 years. Thereafter, there was a low but continuing attrition rate.

In contrast to previous reports of pediatric patients, marked elevation in left ventricular end-diastolic pressure appeared to be a significant risk factor for mortality.

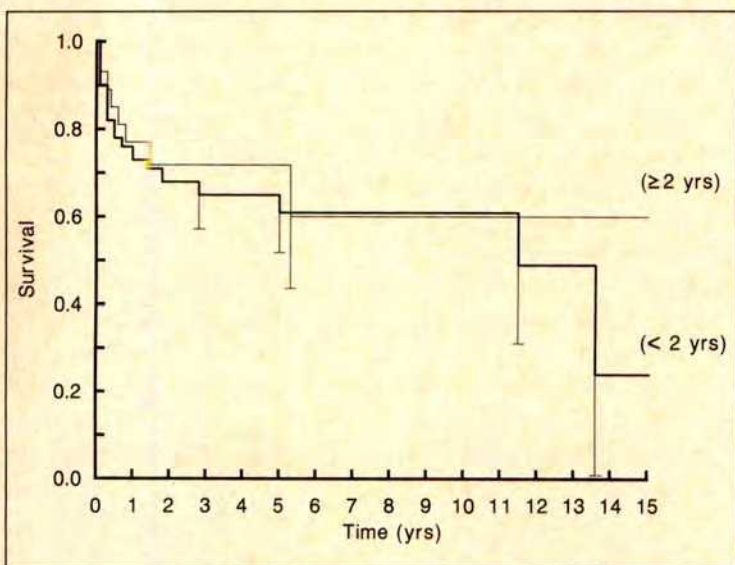


FIGURE 3. Actuarial survival in patients with dilated cardiomyopathy analyzed by age at onset. Solid line represents 53 infants in group 1 who presented at age <2 years, and thin line represents 28 children in group 2 who presented at age >2 years. There is no significant difference between the 2 groups ($p > 0.46$).

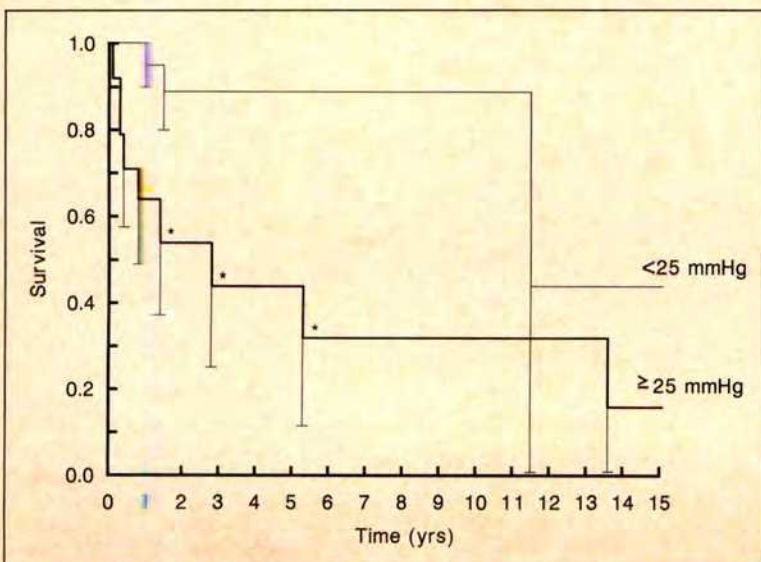


FIGURE 4. Actuarial survival in 44 patients who underwent cardiac catheterization. Four patients who subsequently underwent cardiac transplantation were considered withdrawn alive at the time of transplantation. Solid line represents 16 patients in whom left ventricular end-diastolic pressure was <25 torr, and thin line indicates 28 patients in whom left ventricular end-diastolic pressure was ≥25 torr. The difference between the 2 groups is significant from 6 months to 5 years after onset. * $p < 0.05$.

ty. All but 1 patient with an end-diastolic pressure >25 torr has either died or undergone transplantation. These findings are similar to studies of adult patients in whom mortality is highest in those with marked hemodynamic abnormalities,⁴ particularly elevated left ventricular end-diastolic pressure.³ As in the other reports in children, echocardiographically derived shortening fraction was not helpful in identifying patients who were at higher risk for poor outcome. Whether other load-independent echocardiographic indexes of left ventricular performance are better predictors of outcome remains to be determined.¹³

The development of significant ventricular or atrial arrhythmias, or both, appears to be an additional risk factor for poor outcome. Patients with documented dysrhythmias have a significantly increased risk of dying irrespective of antiarrhythmic therapy. Griffin et al⁷ reported that 71% of their patients who died had known complex atrial or ventricular arrhythmias, or both. The exceedingly high mortality in their patients aged >2 years may have been due, in part, to the development of ventricular arrhythmias in nearly all. This study confirms these observations and suggests that the development of arrhythmias predisposes patients with dilated cardiomyopathy to sudden death. Despite the apparent similarity in left ventricular end-diastolic pressure in patients with and without rhythm abnormalities, the development of atrial flutter/fibrillation or high-grade ventricular dysrhythmias may be an additional indicator of deteriorating ventricular performance.

The 1-year survival for all pediatric heart transplant patients approaches 80% and is higher if neonates are excluded.¹⁴ Currently, the 5-year survival is approximately 60%. Our data suggest that the 1- and 5-year survival for all pediatric patients with dilated cardiomyopathy, irrespective of age of onset, is approximately 75 and 65%, respectively. Therefore, there does not appear to be a compelling reason to proceed with very early cardiac transplantation in pediatric patients with dilated cardiomyopathy based on age alone. In contrast, the 1- and 5-year survival in our patients with a markedly elevated left ventricular end-diastolic pressure was ap-

proximately 64 and 32%, respectively. This subgroup would appear to derive the greatest benefit from cardiac transplantation. Transplantation should be considered within the first 1 to 3 months after initial presentation if it is to have a favorable impact on the rapid decline in the survival rate observed during the first year. Furthermore, the development of atrial flutter/fibrillation or complex ventricular arrhythmias places patients at an increased risk of dying suddenly and may be used as an additional criterion for consideration of transplantation.

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Effects of Immunosuppressive Therapy in Biopsy-Proved Myocarditis and Borderline Myocarditis on Left Ventricular Function

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and Kenneth L. Baughman, MD

Twenty patients with decreased left ventricular (LV) function and endomyocardial biopsy-proved myocarditis (9 patients) or borderline myocarditis (11 patients) were studied to determine whether these 2 histologic subsets of patients with inflammatory heart disease differed in their response to a 6- to 8-week course of immunosuppressive therapy. All patients received a regimen of prednisone, 1.0 mg/kg/day, and azathioprine, 1.5 mg/kg/day, followed by repeat endomyocardial biopsy and reevaluation of LV function. LV function improved significantly in the group with borderline myocarditis, as assessed by LV stroke work—end-diastolic volume ratio (0.26 ± 0.17 to $0.54 \pm 0.31 \text{ kg} \cdot \text{m} \cdot \text{ml}^{-1}$, $p < 0.02$), heart rate corrected velocity of circumferential shortening (0.49 ± 0.30 to $0.80 \pm 0.29 \text{ circ} \cdot \text{s}^{-1}$, $p < 0.05$), and LV ejection fraction (0.30 ± 0.15 to 0.47 ± 0.13 , $p < 0.05$). LV end-diastolic and end-systolic volume indexes also decreased significantly from 129 ± 40 to 94 ± 38 ($p < 0.05$) and 90 ± 37 to $49 \pm 26 \text{ ml}$ ($p < 0.02$), respectively. No significant change in these indexes of LV function or volume occurred in the myocarditis group. Whereas salutary improvements in cardiac output and filling pressures were found in both groups, objective improvement in LV function assessed by complementary indexes of contractility was greatest in the borderline myocarditis group.

It is concluded that short-term immunosuppressive therapy improves LV contractile function and appears to be associated with regression of ventricular dilatation in patients with borderline myocarditis to a greater extent than patients with myocarditis. These data suggest that the patients with borderline myocarditis

may benefit from immunosuppressive therapy and should be considered for inclusion in subsequent trials of immunosuppressive therapy in myocarditis.

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A panel of 8 pathologists met in 1984 to establish standardized criteria for the histologic diagnosis of myocarditis (the Dallas criteria).¹ The goal of the proposed classification scheme was to develop a simple, reproducible set of working histopathologic diagnostic criteria, stressing the importance of both inflammatory infiltrates and histologic evidence of myocyte damage in the diagnosis of myocarditis. Specifically, the investigators define myocarditis as “a process characterized by an inflammatory infiltrate of the myocardium with necrosis or degeneration of the adjacent myocytes not typical of ischemic damage associated with coronary artery disease.” Myocardial inflammatory infiltrates without evidence of concomitant myocyte damage are termed borderline myocarditis under this classification.

A number of previous reports anecdotally described clinical improvement in patients treated with immunosuppressants^{2–8}; however, consistent histologic criteria have not been applied for patient selection in these reports and immunosuppressive therapy has not been standardized. Although the Dallas criteria provide guidelines for the diagnosis of myocarditis at initial endomyocardial biopsy, objective criteria for selection of patients to receive immunosuppressive therapy remain largely undefined. This is in large part due to the paucity of data defining the natural history of myocarditis and correlating initial biopsy histology with therapeutic response to immunosuppressive therapy. To date, immunosuppressive therapy has not been prospectively compared with placebo in the treatment of myocarditis, an essential comparison since spontaneous recovery may occur with only supportive care. Furthermore, it is unknown whether the current Dallas criteria classifications of myocarditis and borderline myocarditis will discriminate between patients responding and not responding to immunosuppressive therapy. The purpose of the

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present study was to determine whether a diagnosis of myocarditis versus borderline myocarditis by the Dallas criteria predicts a differential response to immunosuppressive therapy in a cohort of patients with recent-onset congestive heart failure.

METHODS

Patients: Between January 1983 and January 1987, 185 patients underwent percutaneous right ventricular endomyocardial biopsy as part of an evaluation of new-onset congestive heart failure. Twenty patients were found to have either myocarditis or borderline myocarditis. All patients presented with new-onset heart failure, and at the time of study had evidence of persistent stable left ventricular (LV) dysfunction despite conventional therapy with diuretics, digoxin and frequently captopril. LV dysfunction was defined as abnormal LV function on 2-dimensional echocardiography or radio-nuclide gated blood pool LV ejection fraction <0.40 . Confirmatory evidence of depressed LV systolic function at right-sided cardiac catheterization included cardiac index <2.50 liters \cdot min $^{-1} \cdot$ m $^{-2}$, LV stroke work index <50 kg \cdot m \cdot m $^{-2}$, or abnormal LV filling pressure with mean pulmonary capillary wedge pressure >12 mm Hg.

The initial histologic diagnosis of myocarditis or borderline myocarditis was made by unblinded routine clinical examination of hematoxylin-eosin-stained endomyocardial biopsy specimens. Four to 6 tissue specimens were submitted at each biopsy procedure and were fixed in 10% buffered formalin. Examination of endomyocardial biopsy specimens in our laboratory involves step-sectioning typically at 7 levels so that most of the paraffin-embedded tissue block is examined. Sections are then processed for routine hematoxylin-eosin staining. For the purpose of this study, biopsy specimens of patients with either myocarditis or borderline myocarditis at initial evaluation were reviewed by 2

cardiac pathologists in a blinded fashion using the guidelines established by the Dallas criteria for the assessment of initial biopsy specimens.¹ Semiquantitative assessment of overall severity of cellular inflammatory infiltration (extent of infiltrate score) was graded on a scale of zero (no infiltrate) through 3 (most severe inflammation). Inflammatory cell counts were made at $\times 400$ magnification using a 236×236 μ m graticule. The counts for ≥ 5 randomly chosen fields per specimen were averaged and normalized to an area of 1.0 mm 2 . Inflammatory infiltrates were characterized by inflammatory cell type and focality. Inflammatory infiltrates were considered present when interstitial polymorphonuclear or mononuclear round cells were closely applied to the myocytes in either a diffuse or multifocal pattern not typical of ischemic myocardial damage. Myocyte injury was defined as in the Dallas criteria as either frank necrosis of ≥ 1 myocyte (Figure 1A) or cellular disruption with lymphocytes closely applied to the cell surface. Borderline myocarditis was defined as the presence of inflammatory infiltrates in the absence of myocyte damage (Figure 1B).

All patients underwent initial evaluation including history, physical examination, routine hematology and serum chemistries, screening for collagen vascular disease, pheochromocytoma and thyroid function abnormalities. Coronary arteriography was performed in patients aged >40 years. Right-sided cardiac catheterization was performed at the time of both initial and follow-up biopsy. Cardiac outputs were obtained in triplicate with $<10\%$ variability using a standard thermodilution technique. Percutaneous endomyocardial biopsies were performed with the Stanford-Caves biptome using standard technique.

Seventeen of the 20 patients had technically adequate initial and follow-up M-mode and 2-dimensional echocardiography. Standard M-mode determinations

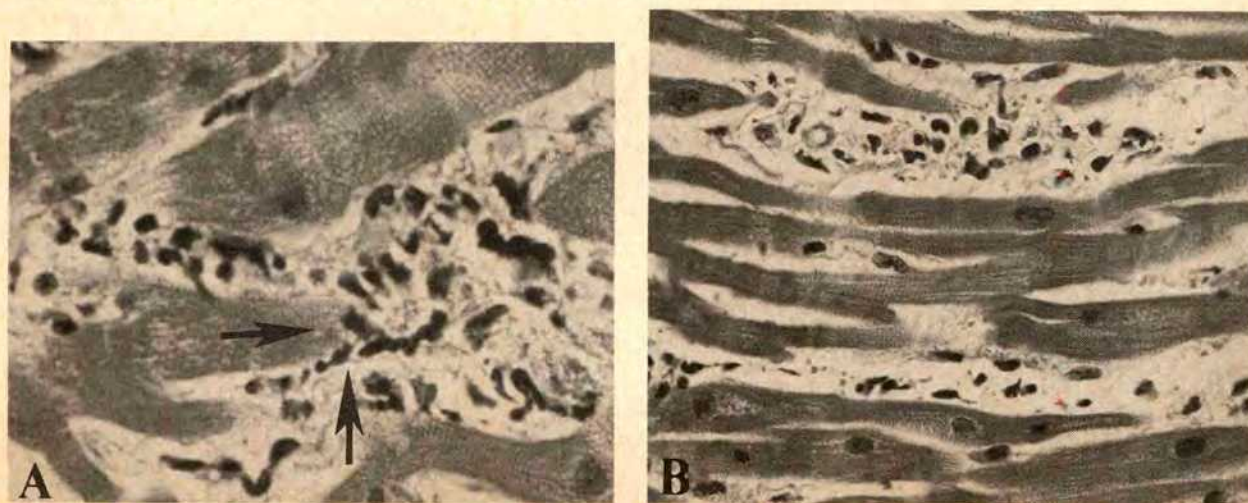


FIGURE 1. Examples of myocyte damage found in myocarditis. **A**, evidence of myocyte damage with closely applied inflammatory cells typical of myocarditis; **B**, typical inflammatory infiltrates of borderline myocarditis without attendant myocyte damage.

of LV dimensions and wall thickness were obtained from each echocardiogram. LV ejection time was measured from the aortic valve profile on the M-mode tracings. Mean velocity of circumferential shortening was calculated from the ejection time and M-mode dimensions and divided by the square root of the simultaneous electrocardiographic RR interval to correct for the effect of heart rate. LV volumes were calculated from the M-mode data using the method of Teichholtz

et al⁹ and were indexed to body surface area. Echocardiographic LV ejection fraction was calculated from these volumes.

Indexes for assessment of objective changes in LV contractile function were chosen to minimize confounding effects of changing loading conditions. LV stroke work index, a highly sensitive but preload-dependent indicator of LV inotropic state, was normalized to LV end-diastolic volume as the ratio of LV stroke work to

TABLE I Hemodynamic and Echocardiographic Data

Pt.	Age (#) & Sex		HR	CI	PCW	EDVI	ESVI	EF	SWI/EDVI	VcFc
Myocarditis										
1	31F	Pre	91	2.60	15	129	93	0.28	0.25	0.73
		Post	84	3.80	10	79	59	0.26	0.76	0.52
2	18M	Pre	79	2.00	28	183	130	0.29	0.11	0.88
		Post	84	4.30	13	—	—	—	—	—
3	50M	Pre	75	2.80	29	92	72	0.22	0.66	0.41
		Post	73	1.80	14	129	72	0.45	0.31	1.05
4	26M	Pre	93	1.80	22	73	38	0.47	0.23	1.43
		Post	94	2.60	7	58	33	0.44	0.53	1.04
5	29M	Pre	111	3.20	20	169	128	0.24	0.15	0.78
		Post	76	3.40	3	121	80	0.34	0.42	0.51
6	56M	Pre	96	2.20	18	132	109	0.18	0.19	0.41
		Post	76	2.50	7	124	86	0.30	0.34	0.72
7	58M	Pre	93	2.50	14	67	34	0.50	0.41	—
		Post	89	2.90	6	106	59	0.45	0.29	1.23
8	22M	Pre	89	2.50	10	172	117	0.32	0.15	0.94
		Post	69	3.00	14	145	116	0.20	0.39	0.34
9	71M	Pre	92	1.80	26	140	131	0.06	0.12	0.20
		Post	62	2.50	12	168	138	0.18	0.25	0.37
Mean										
Pre			91 ± 10	2.38 ± 0.44	20 ± 6	129 ± 43	95 ± 38	0.28 ± 13	0.25 ± 0.18	0.47 ± 0.24
Post			79 ± 10	2.98 ± 0.72	10 ± 4	116 ± 35	80 ± 34	0.33 ± 10	0.41 ± 0.17	0.58 ± 0.20
p Value			<0.05	NS	<0.05	NS	NS	NS	NS	NS
Borderline Myocarditis										
1	31F	Pre	113	2.90	17	112	104	0.08	0.29	0.22
		Post	76	2.90	7	39	14	0.64	1.21	1.42
2	31F	Pre	57	1.80	5	76	39	0.49	0.54	0.77
		Post	68	2.80	10	65	33	0.49	0.60	0.52
3	21F	Pre	120	2.80	24	117	85	0.27	0.20	0.35
		Post	87	3.50	10	97	63	0.35	0.43	0.44
4	38F	Pre	92	2.60	10	76	33	0.56	0.48	1.19
		Post	88	3.00	13	62	32	0.48	0.64	0.93
5	30F	Pre	102	1.80	21	173	134	0.23	0.11	0.61
		Post	64	2.60	6	111	45	0.60	0.43	1.27
6	36M	Pre	84	2.80	10	173	115	0.34	0.20	1.03
		Post	79	4.30	9	101	37	0.64	0.54	1.11
7	21M	Pre	—	—	28	—	—	—	—	—
		Post	—	—	21	—	—	—	—	—
8	37F	Pre	76	1.60	8	161	118	0.27	0.12	0.85
		Post	76	2.30	12	117	77	0.34	0.31	0.74
9	18F	Pre	—	—	23	—	—	—	—	—
		Post	—	—	34	—	—	—	—	—
10	46M	Pre	122	2.40	31	142	96	0.32	0.11	1.13
		Post	124	2.70	10	161	90	0.44	0.16	1.38
11	31F	Pre	94	2.60	22	—	—	—	—	—
		Post	89	2.10	15	—	—	—	—	—
Mean										
Pre			96 ± 20	2.22 ± 0.63	18 ± 8	129 ± 40	90 ± 37	0.30 ± 0.10	0.26 ± 0.17	0.49 ± 0.30
Post			83 ± 17	2.91 ± 0.62	13 ± 8	94 ± 34	49 ± 26	0.47 ± 0.13	0.54 ± 0.17	0.80 ± 0.29
p Value			NS	<0.05	NS	<0.05	<0.01	<0.05	<0.02	<0.05
CI = cardiac index (liters · min ⁻¹ · m ⁻²); EDVI = end-diastolic volume index (ml · m ⁻²); EF = ejection fractions; ESVI = end systolic volume index (ml · m ⁻²); HR = heart rate (min ⁻¹); NS = not statistically significant; PCW = mean pulmonary capillary wedge pressure (mmHg); SWI/EDVI = stroke work-end-diastolic volume ratio (kg · m · ml ⁻¹); VcFc = heart rate-corrected mean velocity of circumferential shortening (circ · sec ⁻¹).										

LV end-diastolic volume. This ratio is an estimate of preload recruitable stroke work, an index of LV contractility exhibiting diminished load dependence without decreased sensitivity to changes in contractility.¹⁰ LV stroke work was calculated from thermodilution stroke volume and pressures obtained at right-sided cardiac catheterization using standard methods.

In contrast to LV stroke work, velocity of circumferential shortening and ejection fraction are largely insensitive to changes in preload, but exhibit afterload dependence. Because systemic vascular resistance index, an index of afterload, remained essentially unchanged in both groups with therapy, these parameters were used without further correction. Combined evaluation of contractile state with indexes of complementary load dependence was performed to limit the potentially confounding effect of changing loading conditions on the assessment of LV function.

After initial evaluation all patients were treated with a 6- to 8-week course of prednisone, 1.0 mg/kg/day, in divided doses, and azathioprine, 1.5 mg/kg/day. On completion of the high-dose regimen, LV function was reassessed with right-sided cardiac catheterization and echocardiography, and endomyocardial biopsy repeated. Prednisone doses were tapered over the following 6 to 8 weeks. Two weeks after discontinuation of prednisone, azathioprine was discontinued. All patients underwent biweekly follow-up study, including complete blood counts. Prednisone doses were not altered during the high-dose regimen; azathioprine dose adjustment was made only for management of uncomplicated neutropenia occurring in 1 patient. The results of the initial and follow-up hemodynamic and echocardiographic assessments are summarized in Table I.

Patients were retrospectively grouped on the basis of the blinded evaluations of the initial endomyocardial biopsy. Statistical comparisons within groups were made with the Wilcoxon matched pairs test. Comparisons between groups were made with the Mann-Whitney U test. Nonparametric statistics were used because of small sample size and failure for many variables to be normally distributed as required for valid use of parametric tests. Proportions were analyzed with the chi-square test. Comparison of the 2 pathologists' histologic rating scores was made with linear regression. The values of the histologic variables used for analysis represent the average of both readers' scores. Statistical significance was achieved when 2-tailed *p* values were <0.05. Group means are expressed as mean \pm standard deviation.

RESULTS

On initial biopsy, 9 of the 20 patients had foci of myocyte damage in addition to myocardial inflammatory infiltrates diagnostic of myocarditis. The remain-

ing 11 patients had borderline myocarditis. The clinical characteristics of the groups with myocarditis and borderline myocarditis did not differ significantly. Mean time from onset of symptoms to biopsy was similar, 7 ± 6 ($n = 5$) weeks in the patients with myocarditis and 7 ± 4 ($n = 7$) weeks in the patients with borderline myocarditis ($p =$ not significant [NS]). In the remaining patients either an insidious onset of symptoms or inability to accurately recall first symptoms prevented determination of time elapsed from onset of symptomatic illness to initial biopsy. Mean captopril dose increased significantly during the course of therapy in the myocarditis group, 35 ± 31 to 44 ± 47 mg ($p < 0.01$) but did not change significantly, 31 ± 45 to 27 ± 32

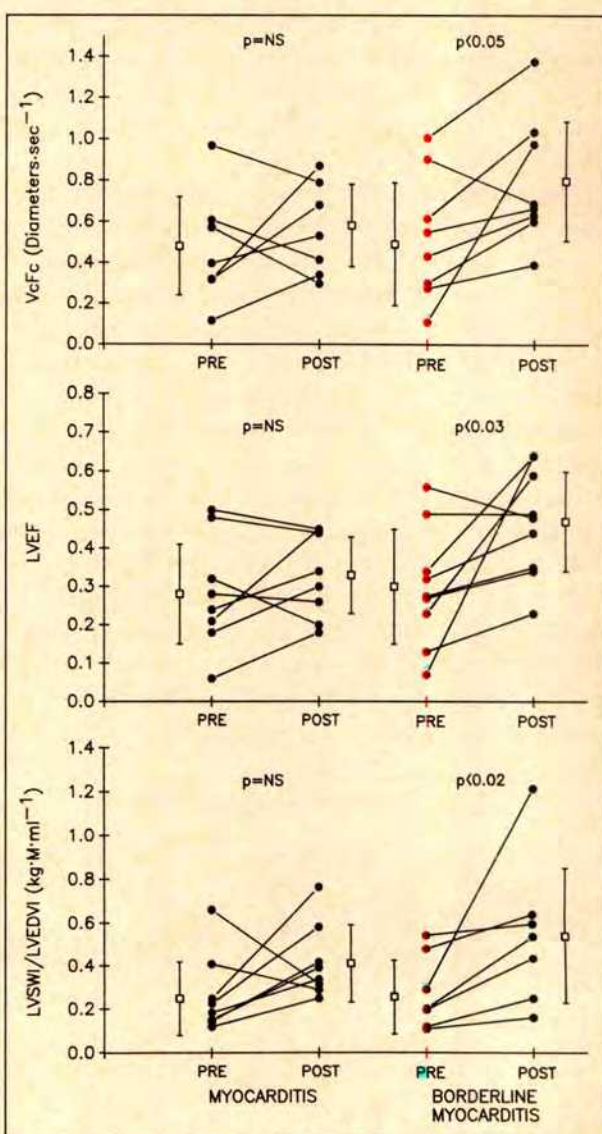


FIGURE 2. Indexes of myocardial contractility at baseline and after therapy: mean velocity of circumferential shortening, corrected for heart rate (VcFc, top panel); left ventricular ejection fraction (LVEF, middle panel); and left ventricular stroke work index divided by end-diastolic volume index (LVSWI/LVEDVI, bottom panel). Significant improvement is obtained with therapy only in the group with borderline myocarditis. NS = not significant.

mg, in the borderline group. On review of the patient records, all captopril dosage increments occurred as a result of dose titration for control of hypertension during prednisone therapy. Systemic vascular resistance index did not change significantly with therapy in the myocarditis group ($2,807 \pm 477$ vs $2,785 \pm 1,108$ dynes \cdot s \cdot cm $^{-5}$ \cdot m 2 [$p = \text{NS}$]) or the borderline group ($3,173 \pm 685$ vs $2,911 \pm 856$ dynes \cdot s \cdot cm $^{-5}$ \cdot m 2 [$p = \text{NS}$]) despite the change in captopril dose.

Echocardiography: Calculated LV volumes decreased significantly in the borderline group but remained unchanged in the myocarditis group. Mean velocity of circumferential shortening increased significantly in the borderline group (0.49 ± 0.30 to 0.80 ± 0.29 circ \cdot s $^{-1}$ ($p < 0.05$)) but remained unchanged with therapy in the myocarditis group (Figure 2, top). Left ventricular ejection fraction increased from in the borderline group (0.30 ± 0.15 to 0.47 ± 0.13 [$p < 0.03$]), and remained essentially unchanged in the myocarditis group (0.28 ± 0.13 to 0.33 ± 0.10) (Figure 2, middle).

Hemodynamics: The hemodynamics of the myocarditis and borderline myocarditis groups did not differ significantly at initial evaluation. Pulmonary capillary wedge pressure decreased significantly in the myocarditis group; however, it decreased to a lesser extent, only approaching statistical significance with treatment in the borderline group. Pulmonary capillary wedge pressure decreased on average to normal with therapy in both groups, but again a significant change of slightly larger magnitude was observed in the myocarditis group. Heart rate tended to decrease with therapy in both groups, but was of statistical significance only in the myocarditis group. Cardiac index increased to a similar extent in both groups, but reached only borderline significance in the myocarditis group ($p = 0.06$).

LV contractility, assessed by the LV stroke work-end-diastolic volume ratio, increased significantly from

0.26 ± 0.17 to 0.54 ± 0.31 kg \cdot m \cdot ml $^{-1}$ ($p < 0.02$) in the borderline group; however, it increased to a lesser and statistically insignificant extent in the myocarditis group from 0.25 ± 0.18 to 0.41 ± 0.17 kg \cdot m \cdot ml $^{-1}$ (Figure 2, bottom). This result is corroborated by similar differences between the 2 groups in echocardiographic ejection phase indexes.

Histology: Assessment of the histologic sections for the presence or absence of myocyte damage occurred with an initial consensus on 39 of 40 biopsy samples. Consensus was reached on independent review of the remaining biopsy specimen. Good correlation between the 2 pathologists' ratings of extent of infiltrate ($r = 0.65$, $p = 0.002$) and inflammatory cells per mm 2 ($r = 0.60$, $p = 0.006$) were obtained. Myocyte damage was found in 11 of 40 biopsy samples. Two patients with myocarditis at initial biopsy had ongoing myocyte damage at the time of the follow-up biopsy.

Initial biopsy specimens in the myocarditis group had histologic findings consistent with more severe inflammatory reaction than found in the borderline group. Initial cell counts were significantly greater ($p < 0.01$) in the myocarditis group and were significantly reduced with therapy, decreasing from 884 ± 385 to 587 ± 211 mm $^{-1}$ ($p < 0.01$). Inflammatory cell counts were only slightly reduced with therapy in the borderline group, from 421 ± 226 to 348 ± 201 mm $^{-1}$ ($p = \text{NS}$). The extent of infiltrate scores paralleled the inflammatory cell counts, with significant reduction in extent scores in the myocarditis group, 1.9 ± 0.6 to 0.9 ± 0.4 ($p < 0.01$). The borderline group had lower initial extent scores without significant change with therapy, 1.3 ± 0.6 to 0.8 ± 0.7 ($p = \text{NS}$).

The fraction of patients with diffuse interstitial inflammatory infiltrates did not differ significantly between the groups either before or after therapy. Mixed polymorphonuclear and lymphocytic infiltrates predominated in the initial biopsy specimens of the myocarditis group (7 of 9 patients). In contrast, only 1 of 11 patients in the borderline group had a mixed lymphocytic polymorphonuclear infiltrate at initial biopsy ($p < 0.003$). After completion of therapy, patients with myocarditis tended to have lymphocytic infiltrates similar to the borderline patients who received treatment. No significant change in the composition of the inflammatory infiltrate occurred with therapy in the borderline group (Figure 3).

Complications of therapy: Insulin-dependent steroid-induced diabetes developed in 2 patients and was managed throughout the course of therapy without difficulty. One patient had an episode of psychosis possibly secondary to the initiation of steroid therapy. Upper gastrointestinal bleeding requiring medical management occurred in 1 patient concurrently treated with oral anticoagulant therapy. Neutropenia complicated

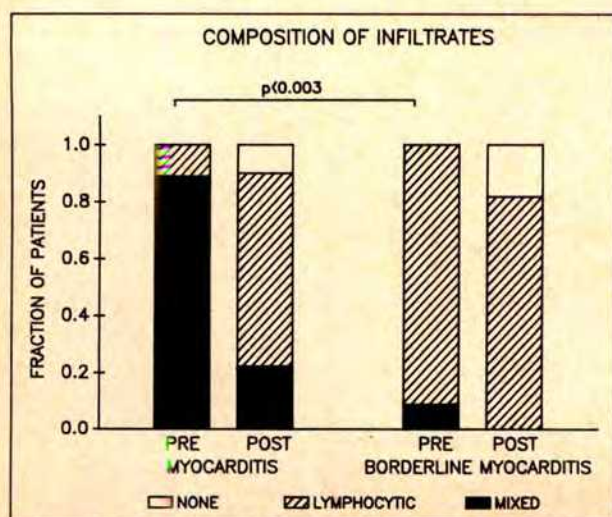


FIGURE 3. Composition of inflammatory infiltrates at baseline and after therapy.

by facial cellulitis was attributed to azathioprine in 1 patient and responded to antibiotics and withdrawal of azathioprine. Mild arthralgias were reported by several patients and were self-limited. One patient developed a mild proximal myopathy which resolved on withdrawal of prednisone. The incidence of these complications did not differ significantly between the 2 groups. There were no deaths or irreversible complications attributable to the immunosuppressive regimen used in this study.

DISCUSSION

The present study represents the largest reported series of patients with histologically demonstrated myocarditis using the Dallas criteria for diagnostic classification undergoing prospective evaluation for objective response to immunosuppressive therapy. Nevertheless, the relatively small size of our study would be insufficient to reach a statistical end point in a comparison of immunosuppressive therapy versus placebo. All patients in our study received a standardized immunosuppressive regimen of azathioprine and prednisone of equivalent dose and duration. Response to therapy was assessed by several indexes of myocardial contractility as well as measures of overall cardiac performance. Contractile function was evaluated with indexes of complementary or minimized load dependence,¹⁰ reducing the likelihood of error in the assessment of contractile function. Concordant changes occurred in all contractility indexes. Small sample size may limit the sensitivity of this study to detect subtle changes in the end point variables; nevertheless, the multiple contractile indexes used should provide reliable assessment of contractile state.

Both the myocarditis and borderline groups demonstrated clinical improvement with immunosuppressive therapy. Indicators of overall cardiac performance improved similarly in both groups with therapy. Further assessment of the response to therapy by indexes of myocardial contractility, velocity of circumferential shortening, ejection fraction, and stroke work-end-diastolic volume ratio, demonstrated significant improvement in the borderline group and no significant change in the myocarditis group. The contribution of conventional therapy with diuretics, captopril and digoxin to this difference in outcome is likely small since all patients received similar regimens that had been stabilized before initiation of protocol therapy with prednisone and azathioprine.

The improvement in contractile function in the borderline group was obtained without significant change in the mean cell count or change in the composition of inflammatory infiltrates with therapy. The myocarditis group showed a trend toward resolution of the acute inflammatory changes; however this occurred without corresponding improvement in contractility. This para-

doxical response to therapy may result from the inability of histologic findings at routine light microscopy to assess the contribution of more subtle immune lesions to myocardial dysfunction, particularly in the borderline group where these lesions may predominate. Several markers have identified either the presence of ongoing viral activity in the myocardium,^{11,12} deposition of immunoglobulin,¹³ or specific autoimmunity to myocardial antigenic determinants¹⁴ including the adenine nucleotide translocator,¹⁵ and cardiac myosin¹⁶ in patients with inflammatory heart disease. Autoimmunity to these determinants may explain the ventricular systolic dysfunction observed in borderline myocarditis without overt histologic myocyte damage. In the murine model of viral myocarditis, a progression of myocardial injury patterns ranging from extensive myocyte damage with intense cellular infiltration of the myocardium in early viral infection to a later phase of chronic myocardial inflammation where cellular infiltration without evidence of ongoing histologic myocyte damage may be observed.¹⁷⁻¹⁹ By analogy, human myocarditis and borderline myocarditis may represent 2 points along a temporal continuum of 1 disease process, with dilated cardiomyopathy as a late sequela.²⁰

If borderline myocarditis represents a phase of subacute to chronic myocardial autoimmunity,¹⁶ it would follow that patients with this lesion should derive greatest benefit from immunosuppressive therapy. Our results support this hypothesis, confirming the findings of earlier studies^{4,20} in which greatest improvement occurred in patients with low-grade chronic myocardial inflammation.

Parillo et al²¹ described the response of patients with chronic dilated cardiomyopathy without evidence of myocarditis with a mean duration of 8 months to a course of high-dose prednisone versus placebo. Fifty nine percent of the 102 patients enrolled were defined as "reactive" by evidence of myocardial gallium-67 uptake, elevated erythrocyte sedimentation rate, or by immunoglobulin, complement, fibroblastic or lymphocytic infiltration of the myocardium at initial endomyocardial biopsy. At the 3-month end point, mean LV ejection fraction increased 5.5% in the prednisone-treated group versus 2.3 percent in the placebo group ($p = 0.035$); however, this modest response was not sustained at 9 months, at which time deterioration of LV ejection fraction occurred in both groups. The Parillo study considers substantially different myocardial pathology, and is not directly comparable to our study with respect to immunosuppressive therapy in myocarditis; rather, it underscores the potential importance of intervention before the development of chronic dilated cardiomyopathy.

The primary limitation of percutaneous endomyocardial biopsy is its potential for sampling error, espe-

cially in inflammatory heart disease where lesions, especially those involving foci of myocyte injury, may be focal or multifocal in nature. A recent report by Hauck et al²² underscores the importance of sampling error in the interpretation of initial endomyocardial biopsy under the Dallas criteria guidelines. They performed multiple postmortem biopsies of the right ventricular apex using a standard biptome, and subsequently compared the results of these endomyocardial biopsy specimens with those of conventional postmortem sections of right and LV myocardium in patients with known myocarditis. Mean lymphocyte counts per square centimeter correlated well between endomyocardial biopsy and conventional histologic slices ($p < 0.0001$); however, false-negative biopsy specimens from the right ventricle ranged from 83% with 1 specimen to 37% with 10. Furthermore, of the 38 patients with autopsy-proved myocarditis, endomyocardial biopsy demonstrated myocarditis was found in only 24 (63%), with borderline myocarditis in 6 (16%) and no diagnostic findings in 8 (23%). Similarly, Dec et al²³ found myocarditis in 4 of 6 patients with borderline myocarditis at initial endomyocardial biopsy who underwent subsequent repeat biopsy. The results of these studies suggest that at least one-third of patients with myocarditis by Dallas criteria may be missed or incorrectly diagnosed as having borderline myocarditis because of the inherent limitations of endomyocardial biopsy.

The histologic and hemodynamic findings in our study suggest that borderline myocarditis may be a separate pathologic entity, potentially responsive to immunosuppressive therapy and analogous to the murine model of myocarditis. Furthermore, many patients with myocarditis by Dallas criteria may be incorrectly given a diagnosis of borderline myocarditis at initial endomyocardial biopsy because of sampling errors. For these reasons, we believe that immunosuppressive therapy in borderline myocarditis deserves further investigation. Our findings reemphasize the limitations of conventional histologic methods and the need for improved techniques for the assessment of myocardial inflammation and autoimmunity.

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Left Ventricular Filling Abnormalities in Asymptomatic Morbid Obesity

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Indexes of left ventricular (LV) diastolic filling were measured by pulse Doppler echocardiography in 16 asymptomatic morbidly obese patients presenting for bariatric surgery and were compared with an age- and sex-matched lean control population. No patient had concomitant disorders known to affect diastolic function. All patients had normal systolic function. LV wall thickness and internal dimension were measured in order to calculate LV mass. Fifty percent of morbidly obese patients had LV diastolic filling abnormalities as assessed by the presence of ≥ 2 abnormal variables of mitral inflow velocity. The ratio of peak early to peak late (atrial) filling velocity was significantly decreased in obese compared with control patients (1.16 ± 0.26 vs 1.66 ± 0.30 , $p < 0.001$). The peak velocity of early LV diastolic filling was significantly reduced in obese patients (75 ± 15 vs 98 ± 19 cm/s, $p < 0.001$). The atrial contribution to stroke velocity as assessed by the time-velocity integral of late compared with total LV diastolic filling was significantly increased in obese patients (36 ± 7 vs $27 \pm 4\%$, $p < 0.001$). Obese patients had significantly increased LV mass (214 ± 45 vs 138 ± 37 g, $p < 0.001$), even when corrected for body surface area (95 ± 16 vs 76 ± 16 g/m², $p < 0.002$). However, increased LV mass did not correlate with indexes of abnormal diastolic filling in obese patients. These data suggest that abnormalities of diastolic function occur frequently in asymptomatic morbidly obese patients and may represent a subclinical form of cardiomyopathy in the obese patient.

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The association between obesity and left ventricular (LV) dysfunction was first recognized over a half century ago.¹ Subsequent clinical and necropsy studies have documented the existence of a cardiomyopathic state associated with morbid obesity.²⁻⁴ Congestive heart failure is a frequent occurrence in the obese patient and is a leading cause of death in the morbidly obese.^{5,6} Despite this observation, relatively few studies have been performed on diastolic or contractile function in the obese. Obesity is associated with a variety of conditions such as atherosclerosis, diabetes mellitus, respiratory disease and systemic hypertension⁷⁻¹⁰ that can affect LV function. Thus, it may be difficult to assess the solitary effect of obesity on myocardial function. We examined a cohort of young, asymptomatic, morbidly obese patients clinically free of these conditions for evidence of LV systolic and diastolic dysfunction using M-mode, 2-dimensional and conventional pulsed Doppler techniques.

METHODS

Patients: Sixteen morbidly obese patients ($>100\%$ or >100 lb [45 kg] over ideal body weight) presenting for gastric bypass operations were compared with 21 lean age- and sex-matched control subjects. Ideal weights were established according to the Metropolitan Life Insurance Company Relative Weight Value¹¹ and converted to metric units.

Patients were selected who met the following criteria (to ensure the exclusion of conditions known to affect diastolic function): (1) age <50 years; (2) no clinical history of angina pectoris or myocardial infarction; (3) no history of chronic systemic hypertension (blood pressure $>140/90$ mm Hg); (4) normal resting electrocardiogram with a normal PR interval; (5) adequate 2-dimensional and pulsed Doppler echocardiographic examination without evidence of valvular disease; (6) heart rate at time of Doppler study between 60 and 100 beats/min (rates outside these limits alter diastolic inflow)¹²; (7) absence of significant pulmonary disease (resting oxygen saturation $>90\%$ or lack of significant restrictive or obstructive defects on pulmonary function tests, and no evidence for right ventricular dysfunction or pulmonary hypertension by 2-dimensional and

TABLE I Echocardiographic Values

Pt. No.	LV Diameter (cm)		LV Mass (g)		LV Mass Index (g/m ²)		Early Filling (cm/s)		Atrial Filling (cm/s)		Early/Late Filling		EF Slope (m/s ²)		Atrial Contribution to Filling (%)	
	O	C	O	C	O	C	O	C	O	C	O	C	O	C	O	C
1	4.6	5.0	188	142	90	83	55	37	65	94	0.86	1.46	2.4	9.2	36	28
2	4.4	4.8	177	118	85	77	73	85	68	63	1.07	1.34	2.9	4.1	42	30
3	4.8	5.1	198	161	96	82	77	91	72	58	1.07	1.59	3.3	3.4	32	27
4	5.3	4.1	288	98	129	65	86	121	54	73	1.61	1.66	3.6	5.9	40	27
5	4.9	5.0	231	129	105	63	85	84	89	66	0.95	1.27	4.0	4.7	41	29
6	4.6	5.0	202	142	81	73	60	90	59	64	1.02	1.41	2.1	3.8	37	32
7	4.6	4.7	184	95	83	56	48	70	63	46	0.76	1.53	1.9	3.5	50	29
8	4.6	4.1	158	78	77	46	69	68	58	43	1.19	1.56	2.7	3.6	32	31
9	5.9	4.7	306	114	124	62	100	112	62	49	1.61	2.27	4.3	4.9	26	21
10	—	4.3	—	112	—	62	75	105	55	49	1.37	2.17	3.7	4.2	27	21
11	4.8	5.1	204	161	96	81	88	110	66	80	1.34	1.38	3.7	6.8	29	33
12	4.3	4.8	206	144	91	92	59	90	52	57	1.13	1.53	3.1	4.3	41	29
13	—	5.4	—	195	—	100	73	80	68	62	1.09	1.27	3.0	4.7	42	33
14	4.6	5.1	211	154	86	80	81	134	62	73	1.31	1.82	3.5	6.9	31	27
15	4.5	5.1	171	147	81	86	79	87	98	62	0.80	1.40	2.5	4.5	45	29
16	5.3	4.9	273	149	111	80	97	99	68	59	1.44	1.67	4.5	5.1	30	27
17	—	5.8	—	222	—	103	—	96	—	55	—	1.71	—	5.2	—	23
18	—	4.2	—	112	—	77	—	120	—	57	—	1.70	—	6.0	—	20
19	—	4.8	—	131	—	69	—	89	—	52	—	2.09	—	4.7	—	24
20	—	5.5	—	186	—	95	—	93	—	46	—	2.02	—	4.3	—	21
21	—	4.7	—	114	—	58	—	106	—	54	—	1.98	—	4.6	—	24
Mean	4.8	4.9	214	138	95	76	75	98	66	60	1.16	1.66	3.2	5.0	36	27
p Value	NS		<0.001		<0.002		<0.001		NS		<0.001		<0.001		<0.001	

C = control subjects; EF = early diastolic flow-velocity peak; LV = left ventricular; NS = not significant; O = obese subjects.

Doppler echocardiography); and (8) normal fasting blood sugar and no history of diabetes mellitus.

A history of cigarette use, hypercholesterolemia (cholesterol >240 g/dl), and family history of heart disease was attained. All patients were normotensive at the time of examination (124/70 mm Hg in control subjects vs 128/76 mm Hg in obese patients). Three patients were taking theophylline preparations and 4 were taking diuretics.

M-mode and two-dimensional echocardiographic examination: Two-dimensional guided M-mode examinations were obtained with an IREX Meridian system utilizing a 3-MHz transducer. Echocardiograms were obtained at end expiration.¹³ Measurements of the internal dimensions of the left ventricle in diastole and systole as well as the thickness of the ventricular septum and the posterior wall were obtained according to the Penn convention.¹⁴ The measurements were recorded just distal to the tip of the mitral valve leaflets at the onset of the QRS complex on a simultaneously recorded electrocardiogram. Mean values were obtained from 3 cardiac cycles using caliper measurements rounded to the nearest millimeter.

LV mass was estimated from septal and posterior wall thicknesses and LV internal dimension in diastole using the formula of Devereux and Reichek¹⁴: LV mass (g) = 1.04 × [(VS + PW + LVIDd)³ −

(LVIDd)³] − 13.6, where VS = ventricular septum, PW = posterior, LVIDd = LV internal dimension in diastole. LV mass calculated in this fashion correlates well with anatomic measurements¹⁴ and is sufficiently reproducible.¹⁵ LV mass was divided by body surface area to derive LV mass index.

Doppler echocardiographic examination: Doppler ultrasound interrogation was obtained with an IREX Meridian scanner equipped with a 3-MHz phased-array transducer. Mitral inflow velocity was recorded from the apical window, and the greatest velocity of diastolic flow distal to the mitral valve anulus was obtained. Doppler signals were recorded at a paper speed of 75 mm/s. The wall filter was set at 0.2 m/s to allow optimal identification of D and F points and signal-to-noise ratios. Mitral inflow patterns were analyzed with a Sony Cardiologic System.

To minimize interobserver variability in the Doppler measurements, tracings of ≥3 cardiac cycles with the highest velocity of early LV diastolic filling were analyzed and averaged. Peak transmitral flow velocity was measured in centimeters per second at the darkest point of the spectral wave forms (peak modal velocity). Diastolic filling intervals were measured in milliseconds with the aid of calipers.

The following measurements were then obtained: (1) peak velocity of early LV filling; (2) peak velocity

of late (atrial) LV filling; (3) slope (descent) of early diastolic flow-velocity peak; (4) ratio between early and late flow-velocity peaks; (5) duration of early diastolic flow; (6) time to peak early diastolic flow; and (7) time to peak and duration of early diastolic flow normalized for heart rate.¹⁶

Diastolic time-velocity integrals were derived by digitizing the area under the diastolic velocity envelope. The early and atrial filling periods were empirically divided at the onset of atrial flow as previously described.¹⁷ The ratio between early and late contributions to diastolic filling and the proportion of LV diastolic filling due to atrial systole were then derived.

Normal limits for these variables were defined as the 95% confidence limits of the distribution of control values (± 2 standard deviations). To ensure a greater degree of accuracy in distinguishing between normal and abnormal inflow patterns, diastolic profiles were considered abnormal in a given subject when ≥ 2 independent variables were beyond normal limits.

RESULTS

Clinical characteristics: There were 13 female and 3 male morbidly obese patients aged 22 to 46 years (mean 38). Their mean body weight was 128 kg (range 99 to 139). On average, the obese patients were 128% and 73 kg over their ideal body weight. All lean control patients fell within the range for ideal body weight according to the Metropolitan Life Insurance Company charts. Both obese and control patients had low cardiac risk profiles. In the obese group there were only 5 smokers and 3 subjects with a significant family history of premature coronary disease. No obese patient had elevated serum cholesterol values.

Echocardiography: Adequate 2-dimensional and real-time Doppler echocardiograms were obtained in all 37 patients. However, in 2 obese subjects, M-mode measurements could not be obtained to assess LV mass. Doppler variables of diastolic function for the control group fell within the normal limits previously determined in other laboratories.^{17,18} No control subject had LV hypertrophy (wall thickness >11 mm).

Mean variables for posterior and septal wall thickness were increased in obese patients (10.4 and 10.1 vs 7.6 and 7.4 mm, respectively). Six of 16 obese patients had LV hypertrophy by echocardiographic criteria. Only 1 of these 6 had LV enlargement (internal dimension >5.6 cm) consistent with eccentric hypertrophy. LV mass index was significantly increased in obese compared with control subjects (95 ± 16 vs 76 ± 16 g/m²); however, no obese patients had an absolute increase in LV mass index (>135 and >112 g/m² in men and women, respectively).¹⁹ All patients had nor-

mal fractional shortening (mean 38%). No wall motion abnormalities were seen in either group.

Doppler values of LV diastolic function are listed in Table I. The early peak velocity was significantly reduced in obese patients (75 ± 15 vs 98 ± 19 cm/s), whereas atrial peak velocity was not significantly changed (66 ± 12 vs 60 ± 12 cm/s). The ratio between early and late flow-velocity peaks was significantly reduced in the obese group (1.16 ± 0.26 vs 1.66 ± 0.30). The slope of early diastolic flow-velocity peak was also diminished in obese compared with control subjects (3.2 ± 0.8 vs 5.0 ± 1.4 m/s²).

The proportion of filling during different phases of diastole as assessed by time-velocity integrals was also

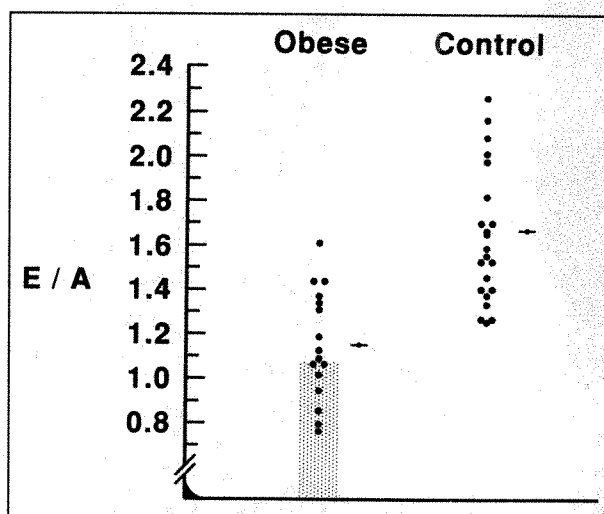


FIGURE 1. Ratio of peak early to peak late or atrial filling velocities (E/A) in 16 obese patients and 21 control subjects. Two dots intercepted by bar, mean values; crosshatches, >2 standard deviations below mean value for control group.

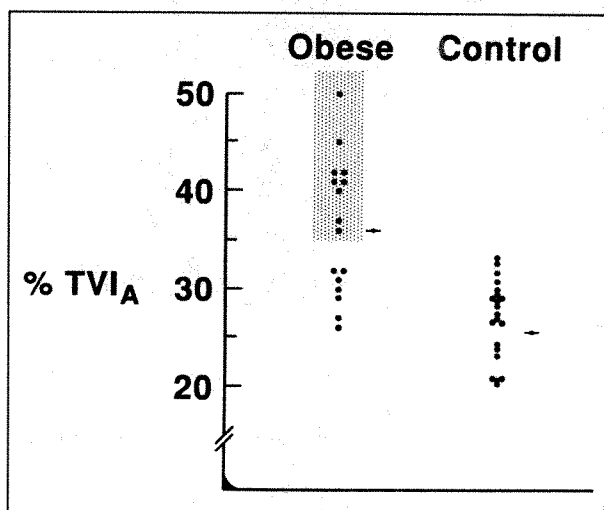


FIGURE 2. Percent of atrial contribution to stroke volume (%TVI_A) in 16 obese patients and 21 control subjects. Two dots intercepted by bar, mean values; crosshatches, values >2 standard deviations above mean value for control group.

highly significant. A significantly increased time-velocity integral of atrial filling combined with a diminished time-velocity integral of early filling was seen in obese compared with control subjects. Thus, the percentage of diastolic filling contributed by atrial systole was significantly elevated in obese patients (36 ± 7 vs $27 \pm 4\%$).

There was no significant difference in heart rates (73 vs 71 beats/min) to account for any of the aforementioned findings. There were also no significant differences in time to peak early filling or total duration of early diastole in obese compared with control subjects. Values did not differ in obese subjects taking diuretics.

In all, 8 of 16 obese patients (50%) had ≥ 2 independent abnormal variables for diastolic function. The 2 most sensitive variables of diastolic function were early and late flow-velocity peak ratio, and percent contribution of atrial to total diastolic filling (Figures 1 and 2). Fifty percent of obese patients had abnormally diminished early and late flow-velocity peak ratios, whereas 56% had abnormally high fractional filling during atrial systole.

Variables of abnormal diastolic function correlated poorly with measurements of LV mass or wall thickness. Only 2 of 6 obese patients (33%) with LV hypertrophy by wall thickness criteria had abnormal diastolic filling parameters. Additionally, only 1 of 4 patients with the highest LV indexes had altered diastolic filling parameters.

By regression analysis, LV mass calculation correlated only with early diastolic flow-velocity peak slope ($r = 0.76$; $p < 0.05$). Paradoxically, greater LV mass was associated with more "normal" rates of deceleration of early transmitral flow. All other parameters of diastolic filling correlated in only a weak inverse fashion with LV mass measurements ($r = -0.16$ to -0.40 ; values $p =$ not significant).

DISCUSSION

In the present study, significant abnormalities of LV diastolic filling were found in 50% of asymptomatic morbidly obese patients compared with lean controls. Abnormalities in LV diastolic filling could not be attributed to abnormal systolic function or other conditions known to impair diastolic filling. Diastolic dysfunction occurs in the morbidly obese patient independent of the development of systemic hypertension, with little or no correlation to LV hypertrophy. As diastolic abnormalities may antedate contractile impairment, noninvasive assessment of obese patients may identify those at risk for the development of congestive cardiomyopathy.

Previous studies: Significant alterations in hemodynamic parameters and cardiac function are invariably seen in morbidly obese patients.²⁻⁴ Increases in blood

volume and resting cardiac output are seen, which correlate with indexes of obesity. Resting heart rate is little changed. Systemic vascular resistance decreases in the normotensive obese patient and is either normal or elevated in the hypertensive obese patient. Preload is chronically increased in obesity, leading to chamber dilatation and hypertrophy to normalize wall stress.

A circulatory congestive state may occur, but its physiologic basis is not well understood. Altered LV chamber compliance has previously been implicated in the pathophysiology of congestive heart failure in obese patients. Abnormal LV diastolic pressure volume relations have been documented in obese subjects with congestive symptoms and prominent LV hypertrophy.²⁰

Relatively little is known regarding diastolic function in obese patients without cardiac symptoms. DeDivitiis et al²¹ suggested that obesity is an important determinant of diastolic filling. They observed reduced LV compliance in 10 asymptomatic morbidly obese subjects. Both LV end-diastolic pressure and A-wave amplitude showed a positive correlation with weight in obese patients.

Recently, Egan et al²² found that relative weight was the single best predictor of peak filling rate as assessed by radionuclide ventriculography. In mildly hypertensive patients, relative weight was a better predictor of diastolic function than was LV mass or wall thickness. Relative weight also correlated significantly with indexes of LV hypertrophy.

Our study suggests that LV diastolic filling abnormalities are common in obesity and bear little relation to LV hypertrophy. The relation between LV hypertrophy and diastolic function appears variable and complex. Although several studies suggest that wall thickness and LV mass are the prime determinants of diastolic filling,^{23,24} diastolic dysfunction may be found in hypertensive patients without significant LV hypertrophy.²⁵ Additionally, elite athletes with "physiologic" hypertrophy may have normal or "supranormal" diastolic filling.²⁶

The relation between obesity and diastolic filling is not well understood. Although the association of myocardial fatty infiltration with obesity is well recognized, it is not a prominent finding at autopsy (3% incidence).²⁷ Similarly, the correlation of diastolic abnormalities and LV hypertrophy was poor in our study. Altered loading conditions are also unlikely to be responsible. Elevated preload is to be expected in obese patients, which would augment early filling.²⁸ As hypertension was absent and diastolic chamber size was normal in our patients, afterload was likely not significantly elevated to account for diastolic abnormalities.

Methodologic considerations and limitations: Pulsed Doppler interrogation of mitral inflow patterns have been previously shown^{18,29} to correlate well with catheter-

terization and radionuclide indexes of diastolic filling. Interobserver variability can be minimized by analysis of multiple cardiac cycles. Accordingly, our control values of diastolic filling were similar to those reported from other laboratories.^{17,18} Furthermore, the credibility of the Doppler technique is enhanced by requiring multiple independent indexes for the definition of abnormal LV filling.

The Doppler technique may also be limited by the absence of an adequate apical window to assess transmitral flow. Doppler indexes may be affected by loading conditions or heart rate, but these values were similar in control and obese patients. In fact, obesity is associated with increased preload, which may increase early peak transmitral velocities.²⁷ Thus, the reduced early peak velocities noted in our obese subjects were present despite potentially higher levels of preload. This could indicate a potentially more profound derangement in LV relaxation or chamber stiffness. Enhanced preload may in fact explain the positive correlation between early diastolic flow-velocity peak slope and LV mass.

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Principles and Practice of Coronary Thrombolysis and Conjunctive Treatment

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The benefits of thrombolysis for treatment of coronary thrombosis and acute myocardial infarction are unequivocal. The only credible mechanism by which thrombolysis confers benefit is recanalization of thrombotically occluded infarct-related arteries. Early recanalization can salvage jeopardized ischemic myocardium. Later recanalization may diminish subsequent arrhythmogenesis, enhance ventricular remodeling, facilitate collateral perfusion, and augment healing even if it does not salvage initially jeopardized ischemic myocardium. Because recanalization is pivotal, because salvage of myocardium is critically dependent on the brevity of ischemia preceding reperfusion, and because salvage of myocardium is the dominant determinant of benefit conferred by thrombolysis, the overall clinical efficacy of coronary thrombolysis depends on the rapidity of induction of recanalization and its persistence.

Despite the consensus that has emerged, some questions remain to be resolved, particularly those relating to relative efficacy of specific agents, optimal dosing regimens and essential conjunctive regimens.

It had been anticipated that the combined Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI)-2 and International Tissue-Type Plasminogen Activator/Streptokinase Mortality Trial, in which tissue-type plasminogen activator (t-PA) was compared with streptokinase with or without subcutaneous heparin, would clarify some of these issues. However, since the study was designed in 1987, a considerable amount of new information has become available that influences interpretation of results. The need for vigorous, early anticoagulation (currently with intravenous heparin) has been recognized and clarified, particularly with respect to maintaining the initially high patency rates elicited with second-generation thrombolytic agents.

PATHOPHYSIOLOGY AND GENERAL MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

Acute transmural myocardial infarction is usually caused by thrombotic occlusion of a coronary artery, often at the site of rupture of an atherosclerotic plaque in a major epicardial vessel.^{1,2} Increased shear forces in blood flowing through high-grade stenoses and activation of platelets and blood coagulation stimulated by subendothelial collagen and tissue factor in atherosclerotic plaques are likely to contribute to thrombosis. Thrombin formed converts fibrinogen to fibrin and activates factor XIII, which cross-links fibrin and stabilizes the clot. It also leads to positive feedback of the coagulation cascade by activating factors V and VIII. Factor Va in conjunction with factor Xa and calcium in association with platelet membrane phospholipids form a prothrombinase complex that generates more thrombin.

Overall management of patients with acute myocardial infarction encompasses measures designed to diminish myocardial oxygen requirements such as reduction of afterload with arterial vasodilators, preload with nitrates and diuretics, and heart rate with β -adrenergic blocking agents, analgesics and antipyretics.³ Enhancement of myocardial oxygenation is critical, however, and best achieved by restoration of perfusion to jeopardized, ischemic myocardium, generally by pharmacologic coronary thrombolysis. This modality involves 2 types of ancillary measures. We refer to adjunctive therapy as interventions targeted toward reducing myocardial injury (such as calcium antagonists, oxygen-centered free radical scavenging, and reduction of myocardial oxygen requirements). We use the term conjunctive to refer to treatment designed to potentiate thrombolysis itself by accelerating or augmenting the extent of clot dissolution, preventing or retarding reocclusion, or both. Conjunctive therapy, then, is designed to increase the rapidity of thrombolysis, increase the frequency of recanalization, and sustain patency after initially successful recanalization. Results of several large clinical trials support the hypothesis that overall recanalization rates are highest among patients treated with thrombolytic agents who are given antiplatelet and anticoagulant conjunctive agents as well.⁴

First-generation thrombolytic agents: Thrombolysis is induced pharmacologically when plasminogen, a cir-

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culating protein that associates with fibrin, is activated to form plasmin, a proteolytic enzyme. Initial attempts to induce thrombolysis clinically involved first-generation thrombolytic agents such as streptokinase and urokinase. These agents are nonspecific in the sense that they convert circulating plasminogen as well as thrombus-associated plasminogen to plasmin with equal alacrity. Thus, they induce degradation of diverse circulating proteins secondary to plasminemia. First-generation thrombolytic agents induce high plasma concentrations of fibrinogen degradation products, while depleting concentrations of circulating fibrinogen, plasminogen, procoagulant proteins, and α_2 antiplasmin (phenomena referred to in aggregate as a systemic lytic state). The fibrinogen degradation products exert anticoagulant and antiplatelet effects and may predispose to bleeding, diminish the likelihood of early thrombotic reocclusion, or both.

Second-generation thrombolytic agents: After the isolation and purification of t-PA in pharmacologic quantities by Collen et al,⁵ it was shown that t-PA and other so-called second-generation agents preferentially convert plasminogen associated with thrombi to plasmin, thus inducing clot lysis with only modest plasminemia.⁶ Degradation of circulating proteins, including procoagulants necessary for hemostasis, is minimal as well. The property of relative clot selectivity is the hallmark of the distinction between first- and second-generation agents. Among the former are streptokinase, urokinase, and anisoylated plasminogen streptokinase activator complex. Among the latter are t-PA and single-chain urokinase plasminogen activator. Clot selectivity has several other implications as well.

PLASMINOGEN STEAL: Plasminogen in plasma is in equilibrium with plasminogen in the fibrin domain. Accordingly, marked consumption of plasma plasminogen such as that induced with first-generation agents leeches fibrin-associated plasminogen from the thrombus into the blood. Consequently, conversion of clot-associated plasminogen to plasmin may be limited, and the rapidity and frequency of recanalization may be attenuated. This phenomenon has been termed "plasminogen steal".⁷ In contrast, induction of clot lysis with second-generation agents that preferentially interact with fibrin-associated plasminogen can proceed without marked reduction of circulating plasminogen. Thus, potential diminution of sustained, intense fibrinolysis can be avoided. This disparity may account in part for the more rapid and more frequent recanalization seen with second- versus first-generation agents.

PROCOAGULATION SECONDARY TO THROMBOLYSIS

Thrombolysis can paradoxically initiate activation of the coagulation system and platelets.⁸ Thus, plasmin

generated by thrombolytic agents can activate coagulation factor V.⁹ Procoagulant effects of plasmin have been recognized also by assay of fibrinopeptide A, a product of action of thrombin on fibrinogen. Elevated concentrations of this peptide have been detected in plasma of patients given fibrinolytic agents, reflecting concomitant induction of procoagulant effects and generation of thrombin activity.¹⁰⁻¹² Concentrations of fibrinopeptide A increase with administration of streptokinase¹¹ or t-PA.¹⁰ However, the increase induced by t-PA is much less pronounced.

Procoagulant effects of fibrinolytic agents mediated by plasmin have been documented under diverse conditions *in vitro* and *in vivo*.¹³⁻¹⁵ Because second-generation agents elicit much less plasminemia than first-generation agents, they are less likely to induce thrombin formation. Conversely, first-generation agents that induce substantial amounts of plasmin elicit greater procoagulant effects, reflected by elevation of fibrinopeptide A, and thus give rise to formation of significantly greater amounts of thrombin. This may explain, in part, the more rapid and more frequent induction of recanalization with second- versus first-generation agents.

It seems clear that the clinical efficacy of coronary thrombolysis depends not only on the intensity and persistence of fibrinolysis *per se*, but also on inhibition of prothrombotic phenomena. The net effect of coronary thrombolysis depends on the relative impact of the induced lytic activity, early procoagulant effects dependent on plasmin and thrombin released from the lysing thrombus, the thrombogenicity of underlying atherosclerotic lesions, the adequacy of heparin-induced anticoagulation, and the extent of endogenous anticoagulation caused by plasmin-induced hypocoagulation and high concentrations of fibrinogen degradation products.

THERAPEUTIC OBJECTIVES

Optimal thrombolytic regimens should induce lysis rapidly and sustain patency. Second-generation agents induce recanalization more rapidly and more often than first-generation agents as judged from the results of the Thrombolysis in Myocardial Infarction trial, phase I¹⁶ and European¹⁷ trials in which 90-minute patency rates for patients treated within 3 hours of the onset of symptoms were 81% for t-PA and 55% for streptokinase. As judged from data compiled from studies of more than 42,000 patients (excluding those in the GISSI-2-t-PA/Streptokinase International trials [see later]), parallel differences in mortality are seen with second- compared with first-generation agents.¹⁸ Early mortality in patients treated with placebo was 11.8% compared with 9.4% in those treated with a first-generation agent and 5.6% in those treated with a second-generation agent. Because of differences with regard to patient selection,

choice of thrombolytic agent and use of adjunctive and conjunctive regimens, and because the comparisons between agents are not direct, such differences, although striking, cannot be considered to be definitive.

IMPORTANCE OF CONJUNCTIVE ANTICOAGULATION

Activation of platelets reflected by an increase in the concentrations of metabolites of thromboxane in urine accompanies clot lysis *in vivo*,^{19,20} despite the fact that neither fibrinolytic agents nor plasmin exert direct effects on washed platelets in the presence of physiologic concentrations of calcium.^{21,22} It may therefore reflect thrombin activity secondary to procoagulant effects mediated by plasmin.²³ Recanalization can be accelerated and augmented not only by inhibition of clot-associated α_2 antiplasmin,²⁴ but also by conjunctive administration of indirect- or direct-acting antithrombin agents such as heparin or hirudin, an experimental recombinant antithrombotic agent.²⁵⁻²⁷ This is consistent with the view that unopposed prothrombotic effects of plasminogen activators retard and impair thrombolysis, and that platelet activation reflects induction of thrombin activity secondary to procoagulant effects of plasminogen activators and to release of thrombin from clots undergoing lysis.

In view of these observations, the clinical efficacy of coronary thrombolysis will be enhanced by (1) intense induction of fibrinolysis for as long as necessary but no longer; (2) use of clot-selective agents that avoid induction of plasminemia; (3) preclusion or attenuation of procoagulant activity that may impede recanalization, precipitate early reocclusion and limit persistence of patency; and (4) use of effective anticoagulants to shift the balance between thrombolysis and thrombosis further toward thrombolysis.

Results of numerous clinical trials attest to the validity of these strategies. Comparisons of studies of thrombolytic agents indicate that mortality is considerably lower when heparin is administered.¹⁸ The impact of heparin is evident also on examination of mortality in control patients given heparin, which was lower than that among patients given a thrombolytic agent without heparin, regardless of the specific activator, as judged from a recent compilation of data from diverse studies.¹⁸ Despite possible differences in patient populations between studies, these findings are highly suggestive.

HEPARIN

Currently, intravenous heparin is the agent used for conjunctive anticoagulation, not necessarily because it is an ideal anticoagulant, but because it is the only parenteral antithrombin presently approved by the United States Food and Drug Administration. Commercial

heparin (a complex glycosaminoglycan) comprises species of molecular weights ranging from 3,000 to 30,000 (mean 15,000). Anticoagulant effects result from the binding of heparin to specific sites on antithrombin III.

At doses that can be used in humans, heparin is only moderately effective when used in conjunction with thrombolytic agents. Limited efficacy may reflect, in part, the relative inaccessibility of fibrin-bound thrombin to heparin-antithrombin III. An approximately 20-fold higher concentration of heparin is required in plasma to inactivate clot-bound thrombin than that needed to inactivate an equivalent amount of free thrombin.²⁸

Hirudin, a direct-acting antithrombin, can inactivate fibrin-bound thrombin. This may explain why heparin is less effective than hirudin in preventing arterial thrombosis in experimental animals.^{29,30}

Despite its limitations, heparin is beneficial in patients given thrombolytic drugs. As shown by Rapold et al,^{10,31} the increase in fibrinopeptide A production seen with coronary thrombolysis can be inhibited by conjunctive administration of intravenous heparin. Their results suggest that heparin diminishes reocclusion by inactivating the free thrombin generated or released in the vicinity of thrombi undergoing lysis.

Although it appears logical to use heparin for conjunctive treatment during and after thrombolysis, questions about the need for this anticoagulant have been raised by the results of the combined GISSI-2/International Study Group trial purported to show that the addition of heparin to thrombolytic agents (i.e., streptokinase and t-PA) did not reduce mortality despite increasing the incidence of bleeding.^{32,33} Although these findings led the author of a recent review to state that "at present, adjunctive heparin therapy is not indicated in patients with acute myocardial infarction who have been treated with thrombolytic therapy,"³⁴ the American College of Cardiology and American Heart Association in their published guidelines strongly recommend the use of heparin in combination with or immediately after thrombolysis.³⁵ This disparity reflects, in our view, a fundamental flaw in the design of the GISSI-2/International Study Group trial regarding heparin. As discussed later, the heparin regimen tested is equivalent essentially to no heparin during the critical interval in which reocclusion must be prevented. Thus, inferences regarding the value or lack of value of conjunctive anticoagulation from trials using suboptimal heparin regimens may not be valid. The lack of effective anticoagulation in such trials may account for suboptimal reduction of mortality in both thrombolytic treatment groups as well as a lack of thrombolytic drug-dependent mortality differences.

Pharmacokinetics: Heparin is eliminated from the circulation by 2 different mechanisms: a rapid, satura-

ble cellular mechanism, and slower, nonsaturable (possibly renal) clearance.³⁶ At lower doses, the saturable mechanism predominates; at higher doses, the nonsaturable mechanism does.³⁷ As a consequence, the half-life of heparin increases with progressively higher plasma concentrations of drug, and recovery in plasma of low doses of heparin is poor.

Results of comparative studies of low-dose heparin (i.e., up to 7,500 U) administered subcutaneously or intravenously indicate that the bioavailability of subcutaneous heparin is in the range of only 23 to 30%. Results of 2 recent clinical trials demonstrated that recovery in plasma over the first 24 hours of high doses of heparin administered subcutaneously (15,000 U twice daily, after an intravenous bolus of 5,000 U³⁸ or 17,500 twice daily³⁹) is substantially less than that after an identical amount given by continuous, intravenous infusion.

After treatment with heparin for several days, the recovery of subcutaneous heparin in plasma increases, presumably because the cellular mechanism of heparin clearance becomes increasingly saturated. Administration of intravenous heparin at a high dose saturates the cellular clearance mechanism much more rapidly.

Various studies both in venous thromboembolism and in myocardial infarction have examined the relation between results of coagulation tests in vitro (such as the activated partial thromboplastin time) after administration of heparin in vivo and the likelihood of recurrent thrombotic events.^{38,40-43} Results indicate an association between the lack of an adequate heparin response in vitro and the occurrence of thrombotic events despite therapy with heparin. Furthermore, the relative risk of thrombotic events in the presence of suboptimal therapy with heparin is increased compared with the event rate with adequate heparin therapy.

Intravenous compared with subcutaneous administration of heparin: Hull et al³⁸ studied patients with venous thromboembolism who were treated with either subcutaneous or intravenous heparin. Despite the slightly lower dose in patients given the drug intravenously, after 24 hours 29% of these patients had subtherapeutic levels compared with 63% of patients treated with subcutaneous heparin. Using a higher starting dose of heparin in both groups, Pini et al³⁹ also noted a significantly lower anticoagulant response in patients randomized to subcutaneous than in patients given intravenous heparin.

Results by Turpie et al⁴¹ in patients with acute myocardial infarction are particularly relevant to interpretation of results of the combined GISSI-2/International Study Group trial and the Third International Study of Infarct Survival in progress. In the Turpie study, patients were given 12,500 U of hepa-

rin twice daily by the subcutaneous route; the anticoagulant effects of the drug were measured daily 6 hours after the injection. On the first treatment day, mean concentration of heparin in plasma was 0.11 U/ml (therapeutic range 0.2 to 0.4 U/ml) and the activated partial thromboplastin time was scarcely prolonged over control values. On subsequent treatment days, mean activated partial thromboplastin time and heparin concentrations increased to just below the lower boundary of the therapeutic range, suggesting that virtually all patients given heparin, 12,500 U twice daily, had heparin levels <0.2 U/ml on the first treatment day and that approximately 50% subsequently had peak heparin levels <0.2 U/ml.

In contrast, results of a prospective study in which heparin was administered intravenously as a continuous infusion at doses of 30,700 U/day after an intravenous bolus dose of 5,000 U revealed an activated partial thromboplastin time >60 seconds (>1.5 times normal) in 82% of patients in 24 hours and in 91% in 48 hours.⁴⁴ The mean heparin dose required to produce an activated partial thromboplastin time exceeding the lower boundary of the therapeutic range was 32,900 U over 24 hours. Thus, in most patients given heparin as an intravenous bolus of 5,000 U followed by a continuous infusion of approximately 30,000 U/24 hours, therapeutic levels occur at 24 hours. In contrast, in those given the same dose subcutaneously (i.e., 15,000 U twice daily after a 5,000-U bolus), anticoagulation will not be adequate in 24 hours. Inadequate anticoagulant effects will be apparent indefinitely in approximately 50% of patients given doses of 12,500 U twice daily subcutaneously.

ASPIRIN

Platelets are prominent components of thrombotic reocclusions after initially successful coronary thrombolysis. Activated platelets can potentiate coagulation, inhibit the conversion of plasminogen to plasmin by releasing plasminogen activator inhibitor from α granules, and inactivate plasmin by releasing α antiplasmin. By activating blood coagulation and elaborating thrombin, platelets indirectly stimulate coagulation factor XIII, which catalyzes the cross-linking of fibrin polymers. Inhibition of platelet activation is thus a target of conjunctive therapy with thrombolysis. One approach is inhibition of coagulation and thrombin, which may account for much, if not all, of the platelet activation seen with fibrinolytic agents. Another is inhibition of specific pathways of platelet activation. The 2 are not mutually exclusive.

The efficacy of conjunctive aspirin was demonstrated in the Second International Study of Infarct Survival (commonly called ISIS-2)⁴⁵ in which, com-

pared with placebo, aspirin alone enhanced survival. Among active treatments, a streptokinase-aspirin combination reduced cardiovascular mortality in the first 35 days by 39% compared with reductions of 25 and 23% for streptokinase and aspirin alone, respectively. The effectiveness of aspirin in this study may have been influenced by the inclusion of patients with incipient rather than evolving infarction (a qualifying electrocardiogram was not required for inclusion) in whom the aspirin may have prevented infarction as it does in patients with unstable angina.

IMPACT OF ANTICOAGULATION ON CORONARY THROMBOLYSIS

In the Third Thrombolysis and Angioplasty in Myocardial Infarction study, patients were given t-PA with or without an intravenous bolus of 10,000 U of heparin.⁴⁶ Coronary angiography performed 90 minutes after the initiation of t-PA demonstrated a patency rate of 79% in both groups. These results were widely interpreted as indicating that heparin did not augment benefit conferred by t-PA. However, by considering only patency at 90 minutes, this trial evaluated only 1 aspect of the speed of thrombolysis rather than early reocclusion. It did not provide information regarding reocclusion and compromise of patency after the 90-minute angiogram. The possibility that heparin would be beneficial by diminishing the incidence of thrombotic reocclusion between 90 minutes and approximately 24 hours after administration of t-PA was addressed in the Heparin-Aspirin Reperfusion Trial. Patients were randomly assigned to either aspirin (80 mg/day) or intravenous heparin (bolus of 5,000 U followed by a continuous infusion of 1,000 U/hour titrated to an activated partial thromboplastin time of 1.5 to 2 times control) concomitantly with t-PA. Patency 18 hours after the onset of treatment was 82% in the heparin-treated group but only 52% in the aspirin-treated group ($p < 0.0001$).²⁸ In a second similar trial, patients treated with t-PA were randomly assigned to either heparin or no anticoagulant.²⁶ Patency 2 days later was 71% in heparin-treated patients compared with only 43% in controls ($p = 0.015$). In a recently completed third trial, patients given 100 mg of t-PA plus aspirin were randomly assigned to either heparin or no heparin.⁴⁷ Patency 2 to 5 days later (mean 81 hours) was 83% with heparin and 75% in the controls ($p < 0.05$). The results of all these angiographic studies are consistent with the following interpretation: Patency 90 minutes after administration of t-PA is dependent largely on the efficacy of the thrombolytic agent itself and not primarily on concomitant anticoagulation, and the persistence of patency induced by t-PA is largely dependent on conjunctive anticoagulation with intravenous heparin. Accord-

ingly, the efficacy of thrombolysis is likely to be compromised by the omission of intravenous heparin.

MORTALITY

Compelling observations indicate that coronary thrombolysis leads to recanalization of infarct-related thrombotically occluded vessels and that early recanalization salvages myocardium and improves outcome. Nevertheless, mortality remains a key criterion of efficacy. Although gains in reduction of mortality on the order of 10% may seem minor, such improvements are significant when viewed in light of the large number of deaths attributable to acute infarction. Yet, because modern treatment of myocardial infarction is accompanied by remarkably low early mortality (compared with experience only a few decades ago), comparative clinical trials require inclusion of huge numbers of patients to detect statistically significant additional reductions in mortality attributable to a specific thrombolytic agent or regimen. It has been estimated that differences in mortality attributable to differences in recanalization rates as great as 50% induced by an agent such as t-PA compared with an agent such as streptokinase might not be reflected by statistically significant (yet clinically important) differences in mortality unless the study population included at least 10,000 patients.⁴⁸ Nevertheless, in an analysis of pooled data of 4 studies that directly compared a first-generation with a second-generation agent in which intravenous anticoagulants were administered, early mortality (i.e., approximately 30 days) was 40% less among patients treated with the second- rather than the first-generation drug.⁴ This analysis excludes results from the recent, combined GISSI-2/International Study Group trial in which intravenous heparin was not used.

Heparin appears to exert a favorable effect on mortality after treatment with thrombolytic agents for acute myocardial infarction. In the Studio sulla Calciparini nell'Angina nella Trombosi Ventricolare nell'Infarto study,⁴⁹ mortality was reduced significantly in patients given subcutaneous heparin (after an initial intravenous bolus) conjunctively with streptokinase compared with that in controls to whom heparin was not given. In the combined GISSI-2/International Study Group trial, the same trend was observed in patients treated with streptokinase and subcutaneous heparin.³² In contrast, no apparent benefit was evident in patients treated with t-PA. This disparity may be explained by the greater early systemic anticoagulant effect produced by fibrinogen degradation products generated by streptokinase, which when enhanced by a modest, later anticoagulant effect of moderate-dose (12,500 U twice daily) subcutaneous heparin may have been sufficient to prevent reocclusion in some infarct-related arteries.

In contrast, because t-PA produces less marked anticoagulant effects, addition of moderate-dose subcutaneous heparin is likely to have been insufficient to prevent reocclusion, especially within the first 24 hours after thrombolysis when a greater number of t-PA-recanalized arteries would be at risk but when the delay in effective anticoagulation would have provided no protection against reocclusion. Thus, a comparison involving patients given only moderate doses of heparin may have been inadvertently biased against t-PA.

In addition, the administration of subcutaneous heparin was delayed in the GISSI-2/International Study Group trial for a minimum of 12 hours after the onset of thrombolysis. Consequently, therapeutic blood levels of heparin were unlikely to have been induced for at least 16 to 20 hours after the onset of administration of the thrombolytic agent. Because as much as 50% of all reocclusion occurs in the first 24 hours after thrombolysis,⁵⁰ it is clear that almost all patients were without effective anticoagulation during the most vulnerable period for reocclusion. Streptokinase has a much longer half-life in the circulation than t-PA. This, coupled with its elaboration of substantially higher concentrations of fibrinogen degradation products with their sustained anticoagulant effects, could account for a more modestly deleterious effect of delayed administration of heparin in patients treated with streptokinase who would presumably be at least partially protected against early thrombotic reocclusion by the presence of high concentrations of circulating fibrinogen degradation products.

The Third International Study of Infarct Survival (ISIS-3), which compares streptokinase, alteplase (double-chain t-PA) and anisoylated plasminogen streptokinase activator complex, entails the same limitations as GISSI-2. Concomitant therapy includes aspirin alone or aspirin plus heparin, but the latter is given only subcutaneously (12,500 U every 12 hours) beginning 4 hours after the completion of administration of the lytic agent. Thus, no significant anticoagulant effect will be elicited until ≥ 8 hours (and probably much longer) after lysis, well past the optimal interval for preventing reocclusion, particularly with the second-generation agent.

It is clear that adequate doses of intravenous heparin prevent reocclusion in patients, as demonstrated in the Heparin-Aspirin Reperfusion Trial, Bleich study, the Sixth European Cooperative Study Group trial,^{25,26,47} and by analysis of pooled data from trials with and without conjunctive intravenous heparin regardless of the lytic agent used.¹⁸ Based on the available information, it is prudent to use intravenous heparin conjunctively with thrombolytic agents as follows: 5,000 U intravenous bolus followed by 24,000 U/24 hours be-

ginning at the completion of infusion of the thrombolytic agent and continuing for 3 to 5 days.

CONCLUSION

The favorable impact of thrombolytic agents in the treatment of acute myocardial infarction is unequivocal. Further progress is likely to result from acceleration of recanalization and diminution or obviation of the biggest single impediment to optimal clinical benefit, namely early, thrombotic reocclusion. The importance of effective anticoagulation in accelerating recanalization and sustaining patency has been documented recently. Ongoing research focuses on improvement of dosing regimens and use of specific thrombolytic agents to maximize fibrinolysis and minimize procoagulant effects and plasminogen steal, development of optimal conjunctive agents, and identification of optimal conjunctive regimens. Progress in the reduction of mortality associated with acute myocardial infarction has been substantial already. Even further reductions can be anticipated.

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Immunosuppressive Therapy and Lipoprotein Abnormalities After Cardiac Transplantation

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The development of hyperlipidemia after cardiac transplantation has been documented by several groups of investigators.¹⁻⁴ Time-related increases in total cholesterol, low-density lipoprotein (LDL) cholesterol, total to high-density lipoprotein (HDL) cholesterol ratio and triglycerides have been described, but the mechanism(s) underlying these changes in lipid profile are less well defined. The administration of prednisone or cyclosporine, or both, is associated with changes in plasma lipoprotein concentrations, and these agents have been implicated in the abnormal lipoprotein profile that develops after cardiac transplantation. However, the relative importance of these drugs in manifest "atherogenicity" is disputed, and this controversy has been highlighted by the conflicting reports of Rudas⁵ and Superko⁶ and their co-workers in a recent issue of this Journal.

Rudas et al⁵ examined factors associated with abnormal lipid profiles and related cumulative steroid dosage to elevations in total cholesterol and triglycerides after transplantation by univariate analysis; the validity of this statistical association is in question, failing to achieve significance by multivariate analysis. Other reports by several groups of investigators ostensibly supporting this view need to be interpreted critically. Three recent studies in patients receiving heart transplants have concluded that corticosteroids are important contributors to post-transplant lipid abnormalities. Taylor and et al⁷ compared lipoprotein profiles at 1 year in subjects on different immunosuppressive protocols, finding prednisone to be the agent most strongly associated with total cholesterol levels. These findings are based on small subgroup analyses of patients undergo-

ing transplantation in different eras and, importantly, this conclusion undermines a more salient observation, namely, the strikingly higher total/HDL cholesterol ratio in patients receiving cyclosporine. Renlund et al⁸ compared the cholesterol levels of 51 patients requiring maintenance corticosteroids with 66 patients who did not. Unfortunately, the details provided regarding corticosteroid tapering and discontinuation are scant, and the demonstration of marked differences between the groups early after transplantation, at a time when most patients continue to take steroids suggests that other factors may be contributing to the observed differences in cholesterol levels. The failure to perform lipoprotein determinations is an even more limiting criticism of this work. The study of Becker et al,⁹ showing an association between total cholesterol, LDL cholesterol and cumulative prednisone exposure, is the most methodologically rigorous of the 3 studies, but represents weak evidence for direct causality. The study is a retrospective review of data generated from a heterogeneous patient population in an uncontrolled, unrandomized fashion and should be noted to contrast in its principal conclusion with earlier observations by the same group.¹ In particular, the reader must be cautioned not to equate such statistical associations with evidence for direct causality on a biochemical or molecular level.

Notwithstanding similar inherent limitations in methodologic design, other studies have failed to find an association between lipid levels and corticosteroid dosage after transplantation.^{2,6} Supportive data in recipients of a renal transplant should be viewed cautiously because the complicated metabolic derangements seen in this population make extrapolation of their lipid abnormalities to patients with cardiac transplants unreliable. Moreover, hyperlipidemia after cardiac transplantation is not representative of the general experience in patients who have had renal transplants. In the latter population hyperlipidemia is characteristically observed before transplantation, and corticosteroid use is most clearly associated with changes in triglycerides after transplantation.^{10,11} These data are supported by studies on lipid profiles in subjects treated with corticosteroids for non-transplant indications. Studies of patients with rheumatic diseases^{12,13} and asthma¹⁴ treated with corticosteroids have consistently demonstrated significant elevations in triglycerides; lesser elevations in total cholesterol and LDL cholesterol were noted in 1

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study in which corticosteroid dosage was also correlated with levels of total cholesterol, HDL cholesterol and HDL subfraction 3.¹³ In a prospective study of the effects of corticosteroids on lipoproteins, the increases in total cholesterol were shown to be a reflection of changes in HDL cholesterol and modest increases in triglycerides. In this investigation, LDL cholesterol was actually noted to decrease by approximately 30%, although this decrement did not reach statistical significance.¹⁵ Importantly, these subjects comprised a heterogeneous group in reasonably good health, exhibited no metabolic disturbances and were taking no other immunosuppressants. The experimental evidence for corticosteroid-induced elevations in triglycerides and HDL cholesterol^{12, 6-18} is, thus, generally born out by clinical experience.

Is this analysis meant to imply that corticosteroids are not contributing to hypercholesterolemia after cardiac transplantation? Not at all; although critical of these published reports, we do not intend to take issue with data suggesting that steroids are an important determinant of hyperlipidemia after transplantation. Rather, we wish to distinguish between the development of hypercholesterolemia and the development of an atherogenic lipoprotein profile. In usual practice, tapering of the prednisone dose is initiated shortly after cardiac transplantation and is, therefore, unlikely to be causal in the concomitant dramatic increases in LDL cholesterol and total/HDL cholesterol ratio that evolve^{2,10} and likely impart a significant risk for the development of atherosclerosis. Similar reasoning can be used to exonerate azathioprine as a cause of post-transplant hyperlipidemia. This drug has been largely succeeded by cyclosporine and is now generally reserved for cases of resistant rejection. Furthermore, there is also evidence showing that azathioprine administration after transplantation is not associated with the development of hypercholesterolemia.¹⁹⁻²²

Increases in cholesterol are to be expected in most patients after cardiac transplantation owing to an improvement in hepatic perfusion and the consequent restoration of hepatic synthetic function. However, the normalization of low pretransplant values should not be (mis)construed as an atherogenic change. In contrast, the generation of true hypercholesterolemia in an otherwise young, healthy transplant population is not compatible simply with an improvement in hepatic perfusion. True hypercholesterolemia indicates the existence of a truly adverse effect of transplantation and its medical management, and highlights the necessary distinction between increases in cholesterol within the normal range and the development of an atherogenic lipoprotein profile.

The effect of cyclosporine on plasma lipoprotein levels has been recently studied in a prospective, double-

blind, randomized, placebo-controlled trial in 36 patients with amyotrophic lateral sclerosis.²³ Significant increases in total cholesterol and LDL cholesterol occurred over a time course reminiscent of that seen after cardiac transplantation. Interestingly, no association was noted between dosage or plasma levels of the drug and the degree of hyperlipidemia. In addition to these data, modern experience with cyclosporine in renal transplants is highly supportive of its potential atherogenicity. Several series have now implicated cyclosporine in post-transplant elevations of total and LDL cholesterol and, less consistently, triglycerides.²⁰⁻²²

We initially hypothesized that cyclosporine-induced hepatocellular toxicity might impair high-affinity receptor-mediated hepatic uptake of LDL leading to elevated serum LDL cholesterol levels.² Similarly, we proposed that the endothelial cytotoxicity of the drug²⁴ would adversely influence triglyceride levels through loss of lipoprotein lipase activity.² However, these hypotheses have not been subjected to rigorous scientific testing. The work of Superko et al⁶ in which changes in hepatic and lipoprotein lipase were observed provides a more plausible explanation for the effects of cyclosporine, and is in keeping with both the commonality of the lipoprotein abnormality after transplantation and the lack of association between drug levels and cholesterol. In this study⁶ the characteristic elevations in triglycerides and in LDL cholesterol seen in cardiac transplant recipients were associated directly with lipoprotein lipase activity and inversely with hepatic lipase activity, respectively. In addition, the cyclosporine dose was shown to correlate with the observed changes in hepatic and lipoprotein lipase activities. Thus, this compelling evidence supports the role of cyclosporine in the development of an atherogenic lipid profile after transplantation. Cyclosporine use is therefore clearly associated with the hyperlipidemia that typifies the cardiac transplant population, and these lipid abnormalities are associated with cyclosporine-mediated variations in essential enzymatic activities central to lipoprotein metabolism. In further support of these observations, Leunissen et al²⁵ reported that cyclosporine therapy after transplantation induced a considerable decrease in hepatic arterial perfusion and an impairment of hepatic synthetic function. The molecular basis for these effects remains to be determined, and one should consider that other potential mechanisms have not been excluded. In this regard, it is perhaps interesting that cyclosporine circulates predominantly bound to cholesterol-rich lipoproteins,²⁶ and its inherent hydrophobicity facilitates its solubilization in lipid membranes, a property that may induce alterations in membrane fluidity and receptor-mediated clearance of LDL cholesterol.²⁷

Accelerated atherosclerosis remains an important cause of morbidity in cardiac transplantation. Evidence

from animal as well as human transplantation suggests that immunologically mediated arterial (endothelial) injury is aggravated by hypercholesterolemia.^{28,29} Thus, the resulting endotheliopathy may further impair peripheral cholesterol metabolism as a result of alterations in endothelial-bound lipase activity. Other factors including age, cholesterol before transplantation, diet, antihypertensive medications and concurrent medical illnesses may also contribute to alterations in lipoprotein profiles in individual patients. The multifactorial nature of hyperlipidemia after transplantation notwithstanding, cyclosporine and prednisone stand out as major contributors; nevertheless, the atherogenic profiles of these drugs appear to be quite different: Cyclosporine induces elevations in LDL cholesterol and the total cholesterol to HDL ratio, whereas corticosteroids are more clearly implicated in elevations of triglycerides and HDL. Future studies should focus on lipoprotein subclass distribution after transplantation and the atherogenic potential of these lipid changes in order to ascertain whether they adversely affect the risk for development of accelerated atherosclerosis. This strategy will be complimented by investigations into the biochemical and molecular mechanisms underlying the hyperlipidemia, as exemplified by the commendable effort of Superko et al.⁶

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Myocardial Malondialdehyde and Uric Acid Release After Short-Lasting Coronary Occlusions During Coronary Angioplasty: Potential Mechanisms for Free Radical Generation

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The stunned myocardium has recently become the focus of considerable interest because of its potential role in negating the benefits of reperfusion. A critical but still unresolved issue relates to the mechanism responsible for this contractile abnormality. In recent years an increasing number of studies have provided indirect evidence that postischemic myocardial dysfunction may be mediated in part by the generation of reactive oxygen species, such as superoxide radical, hydrogen peroxide and hydroxyl radical. These oxygen-free radicals could arise from various sources, such as hypoxanthine conversion by xanthine oxidase, catecholamine degradation and mitochondrial electron transport. Direct evidence of injury by free radicals has yet to be shown in the human heart, but many studies of other mammals have linked reactive oxygen metabolites with myocardial injury.¹⁻⁵ During myocardial ischemia, xanthine dehydrogenase (which appears to be located in the endothelial cells)⁶ is converted to xanthine oxidase, an enzyme that produces superoxide radical, hydrogen peroxide and uric acid from hypoxanthine or xanthine and molecular oxygen.⁷ At the same time, ischemia is associated with rapid catabolism of adenosine triphosphate.⁷ This degradation of adenosine triphosphate causes an efflux of breakdown products that are able to pass through the cell membrane, resulting in an accumulation of hypoxanthine, 1 of 2 substrates for xanthine oxidase. The other substrate (molecular oxygen) is provided by reperfusion, which results in a burst of free-radical generation.⁸ These free radicals initiate chain reactions causing peroxidative breakdown of polyunsaturated fatty acids in the membrane bilayer.⁹⁻¹² The interaction among oxygen-free radicals with polyunsaturated fatty acids has been described as lipid peroxidation and can be measured by formation of malondialdehyde. Until recently, the assessment of alterations in myocardial metabolism in humans early after short and repetitive occlusions of a major coronary artery has not been feasible. However, percutaneous transluminal coronary angioplasty provides a unique opportunity to study the time course of these metabolic changes during transient interruption of coronary flow by the balloon-occlusion sequence in patients with 1-vessel disease and without angi-

ographically demonstrable collateral circulation.¹³⁻¹⁶ In this report we studied the production of hypoxanthine, urate and malondialdehyde during percutaneous transluminal coronary angioplasty.

All patients met the following criteria: a brief history of angina pectoris (<1 year), an isolated obstructive lesion in the left anterior descending coronary artery, and an accessible stenosis of <1 cm in length. All patients were candidates for coronary artery bypass graft surgery because of disabling angina, but were selected for angioplasty rather than surgery because of their anatomy. Ten patients (8 men and 2 women, aged 37 to 72 years) were studied. Of these, 4 were in New York Heart Association class II, 5 in class III and 1 in class IV. In all, the ejection fraction was >50% and none of them had wall motion abnormalities on their left ventriculograms at rest. Four consecutive transluminal dilatations of 90 seconds each with deflation intervals of 3 minutes were performed. All patients gave informed consent and there were no complications directly related to the research procedure.

A Pepine catheter was inserted in the coronary sinus with the end-hole positioned at the origin of the great cardiac vein for blood sampling. Arteriovenous differences of blood hypoxanthine, urate and malondialdehyde were determined at baseline immediately after each balloon deflation and, finally, 5 and 15 minutes after the percutaneous transluminal coronary angioplasty procedure.

HYPOXANTHINE AND URATE: *Great cardiac vein and femoral arterial blood samples were collected in heparinized tubes with equal volumes of cold 154 mM sodium chloride, containing 20 μ M dipyridamole (Boehringer, Ingelheim, Federal Republic of Germany), and 10 μ M erythro-9-(2-hydroxy-3-nonyl) adenine hydrochloride (Wellcome, London, Great Britain). These drugs were used to inhibit adenosine uptake and breakdown. Mixtures were centrifuged in the cold. The supernatant fluids were stored at -80°C . On the day of analysis, these were thawed and mixed with cold 8% perchloric acid. Hypoxanthine and urate were assayed by high-performance liquid chromatography using the method of Huizer et al.¹⁷*

MALONDIALDEHYDE: *After separation of blood cells by centrifugation at 0 to 4°C , the plasma was frozen in liquid nitrogen and stored at -80°C . The malon-*

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TABLE I Vein-Arterial Hypoxanthine Difference in the 10 Patients

	1	2	3	4	5	6
BL	-0.224	0.473	-0.267	-0.446	-0.160	-0.320
Post 1	0.169	0.648	0.805	6.392	0.649	1.990
Post 2	2.606	0.522	2.367	28.410	0.747	1.117
Post 3	1.941	0.891	2.429	23.934	3.039	1.385
Post 4	0.815	3.070	4.163	2.080	0.467	1.510
R5	0.542	-0.069	5.940	0.938	0.562	-0.042
R15	0.336	0.205	6.114	0.415	-0.521	-0.364
	7	8	9	10	Mean \pm SEM	
BL	0.410	0.447	0.847	0.587	0.14 \pm 0.15	
Post 1	3.250	0.467	5.968	0.273	2.06 \pm 0.75	
Post 2	3.160	1.740	2.939	30.910	7.45 \pm 3.72	
Post 3	1.500	4.010	2.160	27.060	6.83 \pm 3.13	
Post 4	-0.978	0.840	1.160	7.441	2.06 \pm 0.75	
R5	-0.010	0.800	-0.660	5.900	1.39 \pm 0.76	
R15	-0.460	-0.300	-0.440	-0.460	0.45 \pm 0.63	

Individual hypoxanthine vein-arterial difference in the 10 patients during baseline (BL), immediately after the 4 percutaneous transluminal coronary angioplasty inflations and, finally, 5 and 15 minutes after the percutaneous transluminal coronary angioplasty procedure (R5, R15).

Post = after; SEM = standard error at the mean.

dialdehyde content of the plasma samples was measured in the presence of 100 μ M ethylene diaminetetraacetic acid as described by Jackson *et al.*¹⁸ The extinction coefficient of the thiobarbituric acid product was taken as 1.56×10^5 M⁻¹ cm⁻¹ for all calculations of the malondialdehyde content.

Values are reported as mean \pm standard error of the mean. Comparison between results before and after percutaneous transluminal coronary angioplasty and occlusion conditions were evaluated using analysis of variance for repeated measurements. When overall significance was found, multiple comparisons were considered significantly different at $p < 0.05$. The relation between uric acid and malondialdehyde arteriovenous difference was evaluated by linear regression analysis.

HYPOXANTHINE PRODUCTION: We studied hypoxanthine production by measuring vein arterial hypoxanthine concentration. Baseline value was $+0.14 \pm 0.15$ μ M. After the first dilatation, vein-arterial hypoxanthine concentration significantly increased to $+2.06 \pm 0.75$ μ M ($p < 0.01$ vs baseline), after the second to $+7.45 \pm 3.7$, after the third to $+6.83 \pm 3.13$, and after the fourth to $+2.06 \pm 0.75$ μ M. Five minutes after the fourth occlusion the vein-arterial difference remained significantly increased ($+1.39 \pm 0.76$; $p < 0.05$ vs baseline), whereas after 15 minutes recovery vein-arterial difference returned to baseline values ($+0.45 \pm 0.63$ μ M; $p =$ not significant [NS] vs baseline). Detailed hypoxanthine production figures of the 10 patients are listed in Table I.

URATE PRODUCTION: We observed a baseline urate vein-arterial difference of $+2.34 \pm 3.12$ μ M. After the first dilatation, urate vein-arterial difference

TABLE II Vein-Arterial Urate Difference in the 10 Patients

	1	2	3	4	5	6
BL	10	7	6	21	-7	4
Postinfl 1	-15	2	6	5	11	5
Postinfl 2	-1	4	-2	2	5	-2
Postinfl 3	-5	6	2	6	19	10
Postinfl 4	5	11	29	6	-28	6
R5	-2	40	43	17	-7	2
R15	-4	5	17	4	-14	-3
	7	8	9	10	Mean \pm SEM	
BL	-6	-9	6.4	-9	2.34 \pm 3.12	
Postinfl 1	-2	-3	2	3.7	1.47 \pm 2.22	
Postinfl 2	3	3.6	5	-2	1.56 \pm 0.95	
Postinfl 3	8	9	-11	13.8	5.78 \pm 2.76	
Postinfl 4	18	19.8	-17	30	7.98 \pm 5.87	
R5	15	29	-14	52	17.50 \pm 7.23	
R15	3	10	-13	8.2	1.32 \pm 3.12	

See legend in Table I.

Postinfl = after inflation; other abbreviations as in Table I.

TABLE III Vein-Arterial Malondialdehyde Difference in the 10 Patients

	1	2	3	4	5	6
BL	-0.32	-0.39	0.96	1.88	-1.67	1.30
Post 1	0.30	1.07	0.83	-0.55	-1.04	1.52
Post 2	1.27	-0.64	-0.1	0.79	1.07	-0.43
Post 3	-1.29	-0.65	3.47	2.73	-0.92	1.06
Post 4	-1.40	-1.00	2.67	2.38	1.5	-1.42
R5	-1.73	1.35	3.5	3.22	-1.48	-2.36
R15	-1.07	0.23	-0.96	-0.23	-0.37	1.39
	7	8	9	10	Mean \pm SEM	
BL	0.10	-1.88	-0.47	-1.71	-0.22 \pm 0.41	
Post 1	0.29	1.19	-1.94	1.73	0.34 \pm 0.37	
Post 2	0.66	1.37	0.31	0.23	0.45 \pm 0.22	
Post 3	0.93	3.60	2.44	-1.44	0.99 \pm 0.63	
Post 4	1.01	1.68	2.22	3.85	1.15 \pm 0.58	
R5	0.59	3.73	5.30	5.28	1.74 \pm 0.91	
R15	-0.63	1.06	-0.96	0.86	-0.07 \pm 0.29	

See legend in Table I.

was $+1.47 \pm 2.22$ μ M (NS vs baseline), after the second $+1.56 \pm 0.95$ μ M (NS vs baseline), after the third $+5.78 \pm 2.76$ μ M ($p < 0.01$ vs baseline), and after the fourth $+7.98 \pm 5.87$ ($p < 0.01$ vs baseline). After 5-minute reoxygenation, vein-arterial urate difference further increased to $+17.50 \pm 7.23$ μ M ($p < 0.001$), whereas 15 minutes after the last inflation, vein-arterial urate difference normalized ($+1.32 \pm 3.12$ μ M, NS). Detailed urate production figures of the 10 patients are listed in Table II.

MALONDIALDEHYDE PRODUCTION: Before percutaneous transluminal coronary angioplasty, vein-arterial malondialdehyde was -0.22 ± 0.41 μ M, after the first dilatation it increased to $+0.34 \pm 0.37$ μ M (NS vs baseline), after the second occlusion to $+0.45 \pm 0.22$ μ M ($p < 0.05$ vs baseline), after the third to $+0.99 \pm 0.63$ μ M ($p < 0.01$ vs baseline), and after the fourth to $+1.15 \pm 0.58$ μ M ($p < 0.01$ vs base-

line). After 5-minute reperfusion, vein-arterial malondialdehyde further increased to $1.74 \pm 0.91 \mu\text{M}$ ($p < 0.01$ vs baseline). Finally, after 15 minutes it returned to baseline levels ($-0.07 \pm 0.29 \mu\text{M}$, NS). Detailed malondialdehyde production figures of the 10 patients are shown in Table III.

The present data show that short repetitive coronary total occlusions of the left anterior descending artery during percutaneous transluminal coronary angioplasty procedure lead to a significant increase of great cardiac vein-arterial concentrations of hypoxanthine, uric acid and malondialdehyde (Figure 1). For malondialdehyde,

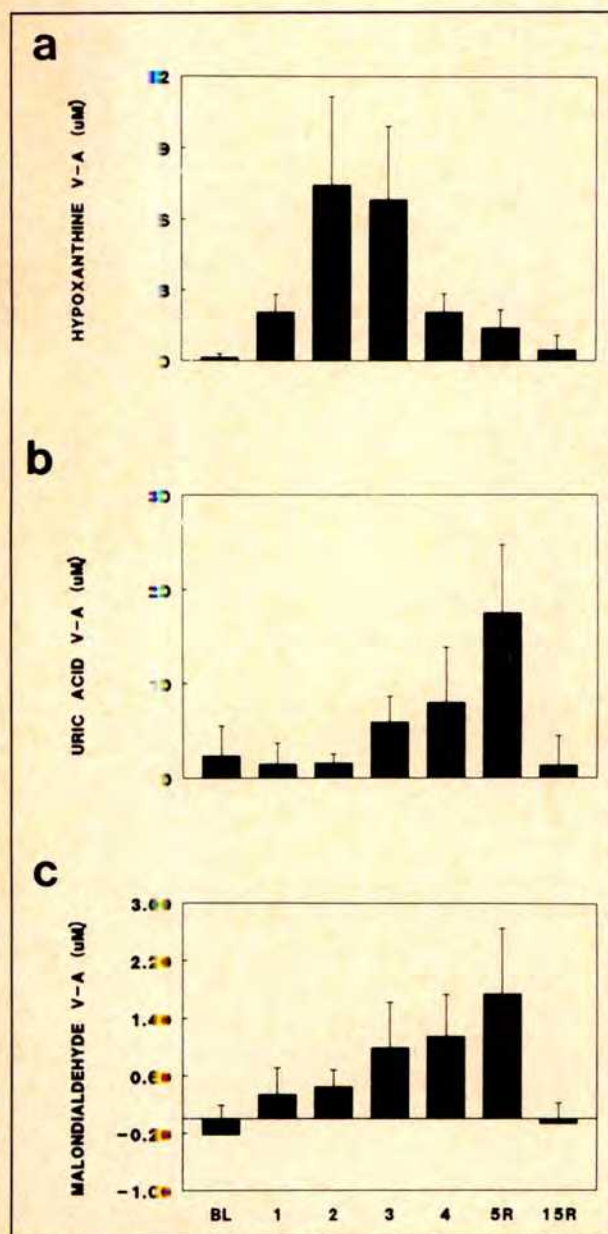


FIGURE 1. Hypoxanthine (a), uric acid (b) and malondialdehyde (c) vein-arterial (V-A) differences during baseline (BL), immediately after the 4 percutaneous transluminal coronary angioplasty inflations and, finally, 5 and 15 minutes after the percutaneous transluminal coronary angioplasty procedure (5R, 15R).

vein-arterial difference showed a progressive increase that peaked 5 minutes after the last inflation. The regression analysis between uric acid and malondialdehyde vein-arterial difference was not significant ($r = 0.34$, NS), which also suggests that other oxygen-free radical sources may play a role. On average, uric acid vein-arterial difference parallels that of malondialdehyde, in contrast to hypoxanthine vein-arterial difference, which peaked around the second and third inflations. Production of malondialdehyde reflects lipid peroxidation, which suggests production of oxygen-free radicals, so the production of malondialdehyde in this model likely results from the generation of oxygen-free radicals.⁹⁻¹² However, malondialdehyde is only one of many products of lipid peroxidation. The reaction between thiobarbituric acid and malondialdehyde produces a pink color that can be measured by spectrophotometry. This assay has been used to study circulating lipoperoxides in many diseases.¹⁹⁻²¹ The assay used in this study usually gives higher malondialdehyde concentrations than are actually present because not only is malondialdehyde measured but also other aldehydes. Furthermore, it measures both preexisting malondialdehyde and all other substances that give rise to malondialdehyde during the assay (in vitro and in vivo). In addition, several chemical species other than malondialdehyde can react with thiobarbituric acid to produce a pink to red color.²² This relative lack of specificity of the thiobarbituric assay has been criticized, but malondialdehyde appears to be produced in a relatively constant proportion to the rate of lipid peroxidation²³; thus, when all samples from 1 patient are assayed simultaneously, the results should reflect the degree of peroxidation. There are several potential sources of oxygen-free radicals during human myocardial ischemia/reperfusion.^{1,24} First, ischemia itself may produce cytotoxic free radicals as a result of reactions involving mitochondrial electron transfer²⁵ after catecholamine degradation by monoamine oxidases, autooxidation or, what is more likely at physiological pH, metal-catalyzed oxidation.^{1,26} Second, the univalent reduction of oxygen by activated neutrophils,^{1,27} though an important source of radicals, is probably not relevant in transient ischemia because it is likely that the chemotactic factors required to promote neutrophil migration into ischemic tissue require several hours for full expression.²⁸ Third, the action of endothelial xanthine oxidase on purine metabolites accumulated during ischemia is another possible system for generating oxygen-free radicals.^{19,29,30} Published data on xanthine oxidase in human myocardium are controversial,³⁰ perhaps owing to the fact that the enzyme can inactivate itself.³¹ We found urate production after angioplasty,¹⁵ but not by isolated perfused human heart.³⁰ The parallel production of urate and malondialdehyde after repetitive coronary occlusions in the angioplasty procedure suggests the possible importance of this

pathway in the production of oxygen-free radicals in the human ischemic heart. These radicals may play a role in the persistence of regional left ventricle dysfunction after reperfusion.

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Waking Up Exhausted as Risk Indicator of Myocardial Infarction

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During the last decade several studies have indicated that sleep problems might belong to the risk indicators for coronary artery disease (CAD). For example, a 6-year follow-up study of >10,000 subjects revealed a risk of 2.04 for CAD in "poor" versus "good" sleepers.¹ Little is known about the types of sleep complaints that are associated with future CAD. One may speculate that trouble falling asleep is

associated with CAD, because this is indicative of prolonged tension. Trouble staying asleep may be predictive for the same reason, or because it is indicative of a heart failure or nocturnal angina. Waking up tired may reflect an impaired sleep or an adverse effect of medication, angina pectoris or aging, and lose its predictive power when adjusted for these factors.

Waking up tired may also indicate depression. Recent meta-analyses of the vast literature of personality factors and CAD have shown that, of all personality attributes, depression is the one most strongly associated with disease outcome.² Because early-morning tiredness is a major characteristic of depression it is predicted that prob-

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TABLE I Database of the Rotterdam Civil Servants Study

	No. of Subjects (%)
Excluded from follow-up due to diagnosed or probable history of CAD at entrance	266 (07)
Missing information (entrance or follow-up)	214 (05)
Angina pectoris (including possible infarction)	54 (01)
Fatal or nonfatal myocardial infarction	59 (02)
Noncardiac or unknown cause of death	74 (02)
Free from CAD during follow-up	3,210 (83)
Total	3,877 (100)

CAD = coronary artery disease.

TABLE II Mean Values of Cardiovascular Risk Factors Among Those With and Without Sleep Complaints

	No. of Subjects	TC (mmol/ liter)	Blood Pressure		Mean Age (yr)
			Systolic	Diastolic	
Trouble falling asleep					
+	620	6.0	140	82	52
0	2,615	6.1	141	82	51
Trouble staying asleep					
+	739	6.1	141	83*	53*
0	2,523	6.1	140	81	51
Waking up exhausted					
+	567	6.1	139*	81	51
0	2,697	6.1	141	82	51
Waking up exhausted without problems falling or staying asleep					
+	247	6.1	138*	81	50†
0	2,898	6.1	141	82	52

*p < 0.05; †p < 0.01.
TC = total cholesterol; + = yes; 0 = no.

lems falling asleep or staying asleep are not predictive of MI when controlled for waking up exhausted, but that the latter complaint remains predictive when controlled for complaints indicating problems in gaining or maintaining sleep (hypothesis I). Waking up exhausted may be a consequence of poor sleep. Statistically controlling for the influence of problems falling or staying asleep does not completely remove any possible effects of these problems on the feeling of being tired at waking up. To rule out any possibility that exhaustion on waking up is caused by a "bad night," we also tested the hypothesis that those who wake up exhausted but do not have problems falling or staying asleep are at increased risk of myocardial infarction (hypothesis II).

The test of these hypotheses requires a prospective study. Such a study was conducted in Rotterdam. The cohort was formed by 3,877 male city employees, aged 39 to 65 years, who participated in a voluntary health check-up. Tests included blood pressure, cholesterol, smoking habits and angina pectoris by means of the Rose questionnaire. A resting electrocardiogram completed the cardiovascular screening. At screening,

all subjects completed form A of the Maastricht questionnaire. The Maastricht questionnaire is a scale for assessing "vital exhaustion," a state characterized by feelings of excess fatigue and loss of energy, increased irritability and demoralization. This scale included 3 sleep questions: "Do you often have trouble falling asleep?", "Do you wake up repeatedly during the night?" and "Do you ever wake up with a feeling of exhaustion and fatigue?" Each question was followed by Yes-No.

The cohort was followed during an average period of 4.2 years. Cause of death was obtained from the death certificates. Nonfatal myocardial infarctions were documented by electrocardiographic and serum enzymatic evidence. A detailed description has been given elsewhere.³

Hypothesis testing was accomplished by means of the Mantel-Haenszel test for stratified data. Analyses were performed by means of dichotomous groupings (sleep complaint absent-present, a question mark being coded as indicating the presence of a complaint). The second hypothesis was tested by a multiple logistic regression, controlling for systolic blood pressure, cholesterol, age, smoking, and the use of antihypertensive drugs.

Feelings of excess fatigue have been found to belong to the short-term precursors of myocardial infarction and sudden death in many retrospective studies. Therefore, we also analyzed the association between waking up exhausted and myocardial infarction against length of time interval.

The database of the follow-up study is presented in Table I. It shows that 59 well-documented fatal or nonfatal myocardial infarctions occurred among the 3,269 subjects free from CAD at entrance. Two hundred sixty-six subjects were excluded from the follow-up analyses because of prior myocardial infarction according to the electrocardiogram (Minnesota code I 1.2) or present angina pectoris.

Among those free from CAD at entrance, 4 subjects underwent bypass surgery, and 5 subjects had angina pectoris, including possible myocardial infarction. Because of insufficient documentation, this group was not included in the group of new cases.

Eighty-three percent of the participants of whom all information (entrance or follow-up) was available remained free from CAD. They form the reference group with which the 59 documented cases will be compared.

Table II lists the absolute number of people who endorsed a sleep complaint and the association of each complaint with the classic risk factors. The groups did not differ meaningfully with regard to mean levels of the somatic risk factors, although it

remains interesting to note that those who said that they wake up exhausted and fatigued without problems falling or staying asleep were somewhat younger and had a slightly lower systolic blood pressure. Heavy smoking had a moderate positive association with sleep complaints. Problems falling asleep were found to increase the risk of myocardial infarction by 87% ($p < 0.05$). Controlling for waking up exhausted reduced the risk by 33%, to a level which is no longer significant. Problems staying asleep increased the risk by 38% ($p < 0.25$). Controlling for waking up tired reduced this association to almost nil. Waking up exhausted doubles the risk of future myocardial infarction (crude RR = 2.1; 95% confidence interval 1.2 to 3.5). The risk was slightly reduced to 2.0 when controlled for the other sleep complaints, but remained significant. These findings confirm the first hypothesis.

The reduction of "exposed" subjects to those who felt exhausted on waking up only resulted in a decrease of the number of cases to 50 and of the number of non-cases to 2,879. In this analysis the relative risk was found to be 2.6 (95% confidence interval 1.3 to 5.1). Waking up exhausted in the absence of the 2 other sleep complaints remained predictive of myocardial infarction in the multivariate analysis. The relative risk increased slightly to 2.7 (95% confidence interval 1.3 to 5.8), due to the negative association between this sleep complaint and age and systolic blood pressure. This finding confirms the second hypothesis.

The analysis of the association between waking up exhausted and myocardial infarction against length of time interval showed a clear decrease of the association. The relative risk was 6.5 for the first year of follow-up and decreased to 2.3, 2.3 and 1.8 for the second, third and fourth year of follow-up, respectively.

The main results of this study support the hypothesis that sleep problems, and especially being exhausted on waking up, belong to the precursors of myocardial infarction.

The study was not designed as a systematic study about sleep problems as risk indicators for myocardial infarction. Such a study should have included more questions about each of the 3 sleep problems, sleep duration and how long sleep problems were present. Any conclusion should be limited to the finding that those who report exhaustion on waking up are at increased risk of myocardial infarction. Waking up exhausted may be a consequence of poor sleep. Interestingly, the relative risk of waking up exhausted increased 50% when those with problems falling or staying asleep were excluded from the analyses. This makes it seem rather unlikely that early

morning exhaustion caused by problems falling or staying asleep has any predictive power.

Because of the lack of additional information about the medical and psychological condition of the participants, it is difficult to explain the association observed. Because those who had past or current CAD at the screening were excluded from the analyses, it can be ruled out that the association was due to a clinically manifest CAD. The multivariate analysis showed that the association could not be attributed to the standard risk factors either.

Perhaps exhaustion on waking up is a marker of subclinical heart disease. This interpretation is supported by the decline of the association during follow-up. However, the prevalence of waking up exhausted in the group with electrocardiographic evidence of CAD at entrance was similar to the prevalence of this complaint in the group free of CAD. Recent findings of a study of patients with percutaneous transluminal coronary angioplasty indicate that improved perfusion does not result in a meaningful decline of exhaustion scores (Kop WJ et al, personal communication).

The results of this study can also be interpreted as supporting the hypothesis that a period of depression often precedes the onset of myocardial infarction. Several studies have observed a positive association between depression and future myocardial infarction.^{4,5} However, the nature of the relation between depression and the occurrence of cardiac events is unclear.

Waking up tired is an element of the syndrome of vital exhaustion. However, this complaint was found to make a unique contribution to the assessment of this syndrome. When the logistic regression analysis was repeated including form A of the Maastricht questionnaire (without the sleep complaints) both "waking up exhausted in the absence of other sleep complaints" and the questionnaire were independently associated with future myocardial infarction.

Both interpretations (marker of subclinical CAD or marker of subclinical depression) are not necessarily mutually exclusive. Rozanski et al⁶ showed that mental stress may induce silent myocardial ischemia in patients with CAD. The somatic and mental condition may interact. Perhaps the threshold for myocardial ischemia due to mental stress in patients with subclinical levels of CAD is especially low among those who are exhausted because of prolonged tension.

The observed association should also be interpreted cautiously because sleep apnea may be a confounder. Recent studies have drawn attention to sleep apnea as a possible determinant of myocardial infarction and sudden death.¹ Patients with this disease complain about feeling tired on waking up too. Because the presence of sleep apnea can only be confirmed in hospitalized pa-

tients, it was impossible to control directly for this possible confounder.

In the absence of additional information it is impossible to decide whether waking up exhausted in the absence of other sleep complaints reflects a subclinical heart disease or an exhaustion-depression syndrome. However, the strength of the association supports the belief that this complaint merits attention in cardiovascular research.

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A New Noninvasive Method for Estimation of Pulmonary Arterial Pressure in Mitral Stenosis

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The appearance of an increased pulmonary artery (PA) pressure is an important moment in the clinical history of mitral stenosis. A direct measurement of PA pressure levels is possible only with right-sided cardiac catheterization. This technique, being invasive is not risk-free and, consequently, many noninvasive methods for the evaluation of PA pressure have been proposed.¹ These procedures usually lack sensitivity and are limited in their ability to detect and quantify mild to moderate modifications of PA pressure. The introduction of Doppler echocardiography allowed the development of new procedures.²⁻⁶ Unfortunately this method is not applicable in the absence of Doppler-detectable tricuspid regurgitation.⁷ Furthermore, the computed systolic PA pressure value is approximate because a clinical estimation of the right atrial pressure is necessary. Moreover, a good acoustic window and satisfactory flow tracings are indispensable. To avoid the aforementioned drawbacks we attempted a different approach to the noninvasive estimation of PA pressure, devising a method based on the modifications induced by an increased PA pressure on the power spectrum of the pulmonary component of the second heart sound. We used fast-Fourier analysis to examine the acoustic characteristics of this heart sound and to define its frequency distribution in patients with normal and increased PA pressure to search for a relation between the PA pressure level and the spectral characteristics of the pulmonary component of the second heart sound.

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The study population consisted of 30 patients, 14 men and 16 women, aged 17 to 73 years (mean average \pm standard deviation 55 ± 12), who underwent a clinically indicated cardiac catheterization; 16 patients were affected by mitral stenosis, 13 had systolic PA pressure > 34 mm Hg. The patients were classified into 3 groups according to the values of systolic PA pressure (Table I). A phonocardiogram was recorded during held expiration at the second left intercostal space near the sternal border, where the second heart sound was best revealed. The pulmonary component was readily identifiable in all patients using the dirotic notch of the simultaneous carotid pulse or aortic valve closure, or both, on M-mode echocardiogram. The signal was recorded with a piezoelectric microphone having a flat response curve between 7 and 1,000 Hz and was passed through a T-type Maass & Weber filter, with a cutoff > 650 Hz. The phonocardiographic tracing and a reference electrocardiographic lead II were simultaneously digitized employing an 8-bit analog/digital converter connected with a 6510 microprocessor. The sampling frequency was 1,282 Hz per channel, yielding a 641-Hz Nyquist limit frequency. The data files were preprocessed to demean in order to delete the continuous component of the signal. The pulmonary component of the second heart sound was extracted with an interactive program using a Hanning window of 69 ms operated on the data file. The window was surrounded with 0-padding data building up a data record of 512 points (400 ms). This record was then analyzed using the fast-Fourier transform that yielded the amplitude-frequency spectrum ranging from 0 to 641 Hz at 2.5-Hz intervals. Mean frequency spectrum of each pa-

TABLE I Summary of Patient Data

Case	Age (yr)	SAP	Measured PAP			Fn	Q factor	Estimated PAP		
			S	D	M			S	D	M
Group A (systolic PA pressure < 30 mm Hg)										
1	17	120	24	10	18	28	0.73	20	5	11
2	45	120	25	7	16	40	1.25	32	14	21
3	49	145	25	8	10	58	0.8	26	9	15
4	51	135	25	10	18	23	0.95	23	8	15
5	52	110	30	21	23	43	0.89	28	9	17
6	53	158	26	8	14	75	0.8	30	10	16
7	55	140	28	9	18	45	1.12	30	12	19
8	55	150	30	15	19	28	0.95	24	8	14
9	55	140	30	15	20	40	1.0	28	11	18
10	56	135	30	15	23	33	1.34	33	15	23
11	63	140	25	10	13	43	1.0	28	11	18
12	63	118	24	11	18	50	0.65	22	6	11
13	64	140	25	8	14	48	1.19	32	14	21
14	65	140	25	10	15	43	0.69	21	6	11
15	65	150	28	12	18	50	1.0	29	11	18
16	70	160	25	10	15	40	1.0	27	10	17
17	73	130	22	8	13	35	0.78	22	7	12
Mean	55	137	26	11	17	42	0.94	26	10	16
± SD	± 12	± 14	± 2	± 4	± 4	± 12	± 0.19	± 4	± 3	± 4
Group B (systolic PA pressure ranging from 31 to 40 mm Hg)										
1	48	100	35	10	22	70	1.06	34	14	21
2	50	147	34	13	21	53	1.52	41	20	28
3	56	115	40	12	20	123	0.95	42	16	23
4	62	140	35	10	23	55	1.0	30	12	19
5	64	160	35	12	17	55	0.82	30	11	18
Mean	57	132	36	11	21	71	1.06	35	14	22
± SD	± 7	± 24	± 2	± 1	± 2	± 30	± 0.26	± 6	± 3	± 4
Group C (systolic PA pressure > 41 mm Hg)										
1	32	105	90	60	75	123	3.45	94	56	74
2	33	120	45	18	25	75	1.5	45	21	30
3	53	152	44	15	32	103	1.03	40	16	24
4	53	125	50	18	25	60	1.69	46	23	32
5	56	145	42	28	22	125	1.1	45	19	27
6	59	120	90	60	75	190	2.38	84	45	59
7	67	210	50	10	15	110	1.7	55	27	37
8	67	112	75	31	51	158	2.24	75	40	53
Mean	52	136	61	30	40	118	1.88	60	31	41
± SD	± 13	± 34	± 21	± 20	± 24	± 42	± 0.79	± 20	± 14	± 18
D = diastolic; Fn = frequency peak; M = mean; PAP = pulmonary artery pressure; S = systolic; SAP = systolic aortic pressure; SD = standard deviation.										

D = diastolic; Fn = frequency peak; M = mean; PAP = pulmonary artery pressure; S = systolic; SAP = systolic aortic pressure; SD = standard deviation.

tient was obtained by averaging 8 spectra.^{8,9} Two acoustic parameters were considered: (1) the frequency peak (Fn), represented by the frequency associated with the maximal amplitude of the spectrum; and (2) the quality of resonance (Q factor). The Q factor is a measure of the sharpness of resonance of a vibratory electrical or mechanical system having a single degree of freedom, or more simply is a measure of the capability of the system to resonate with a main frequency.^{10,11} The Q factor increases with the structural homogeneity of the vibrating system and can be computed from the following equation: $Q \text{ factor} = Fn / (F2 - F1)$, where Fn represents the frequency peak of the spectrum and (F2-F1) represents the difference

between the frequency values above and below Fn, respectively, for which the amplitude of the spectrum falls to 50% of the peak value. The values of the Q factor are related to the characteristics of the setup used to analyze the frequency and could vary with the type of equipment. The Student t test was performed for Fn and the Q factor among the 3 groups. In addition, Fn and the Q factor were correlated with systolic, diastolic, mean PA pressure, the systemic systolic pressure, the heart rate and the age of each patient. Statistical analysis was performed using linear and multiple regression analysis and standard programs. Statistical significance was accepted at the probability level $p < 0.001$.

The mean amplitude versus frequency spectrum of the pulmonary component of the second heart sound obtained in group A is displayed in Figure 1a. It was mainly composed of frequencies <200 Hz. Peak amplitude was 22 ± 12 Hz, the average Q factor was 0.94 ± 0.19 . Mean frequency spectrum of group B is shown in Figure 1b. Peak frequency was 71 ± 30 Hz and the average Q factor was 1.06 ± 0.26 . Mean frequency of group C is displayed in Figure 1c. Frequency peak was 118 ± 42 Hz. The average Q factor was 1.88 ± 0.79 . The Student t test performed between group A and group C was significant for both Fn ($t = 6.95$; $p < 0.0001$) and the Q factor ($t = 4.68$; $p < 0.0001$). No

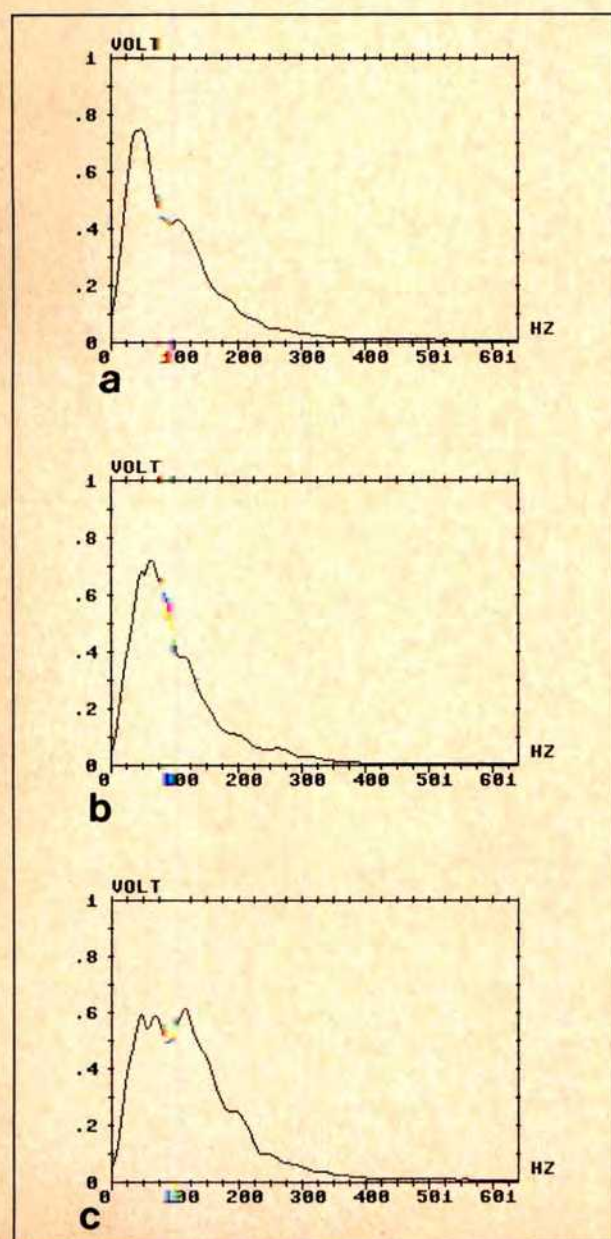


FIGURE 1. Mean frequency spectrum of group A (a), group B (b) and group C (c). Amplitude, vertical axis; frequency, horizontal axis.

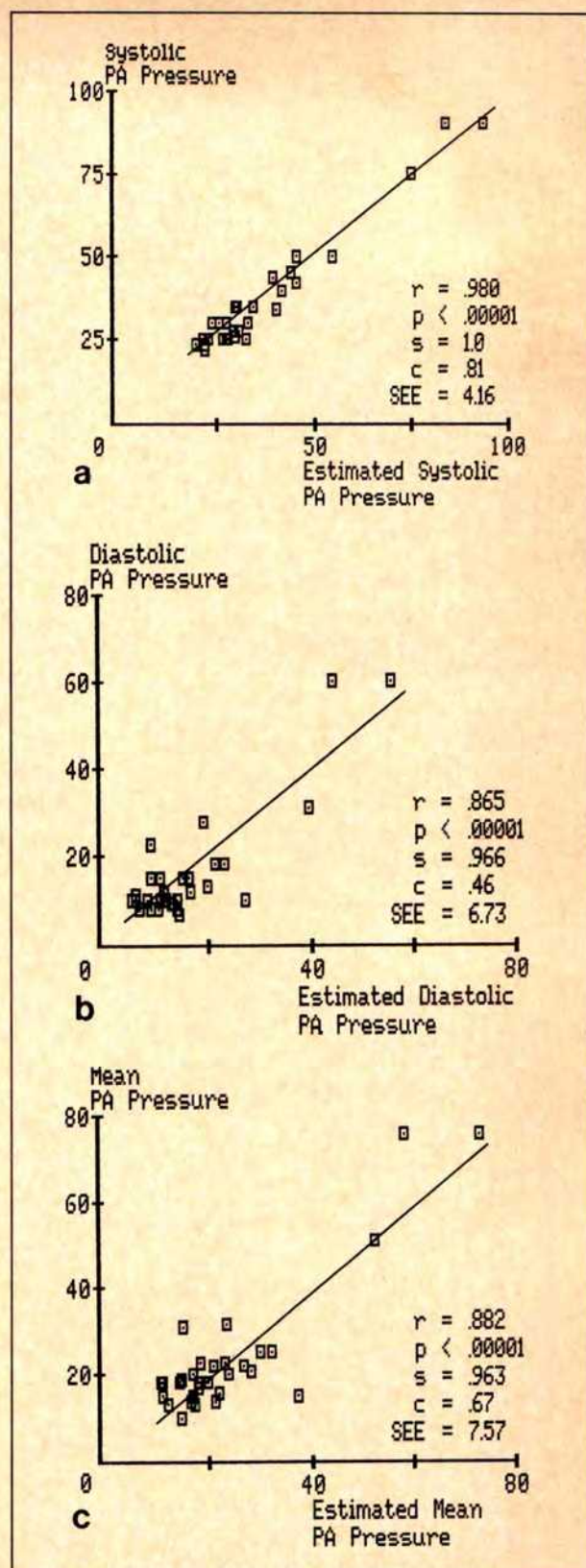


FIGURE 2. The systolic (a), diastolic (b) and mean (c) pulmonary artery (PA) pressures measured with right-sided cardiac catheterization are displayed on the vertical axis (mm Hg) and the corresponding estimated values on the horizontal axis (mm Hg). The correlation lines overlap the identity lines; c = constant; p = probability level; r = correlation coefficient; s = slope; SEE = standard error of the estimate.

significant differences were found for Fn and the Q factor between groups A and B and between groups B and C. Highly significant correlations were found for Fn with systolic ($r = 0.857$, $p < 0.0001$), diastolic ($r = 0.721$, $p < 0.0001$) and mean ($r = 0.726$, $p < 0.0001$) PA pressure. On the contrary, no significant relations were found between Fn and systemic systolic pressure, Fn and age, and Fn and heart rate. The correlation coefficients between the Q factor and PA pressure also showed a good linear relation for systolic ($r = 0.909$, $p < 0.0001$), diastolic ($r = 0.833$, $p < 0.0001$) and mean ($r = 0.833$, $p < 0.0001$) PA pressure. No significant relations were found with systemic systolic pressure, age and heart rate. Figure 2 shows the values of the multiple regression analysis performed with systolic (Figure 2a), diastolic (Figure 2b) and mean (Figure 2c) PA pressure as a dependent variable and Fn and the Q factor as independent ones.

The results of the frequency analysis indicate that the frequency composition of the pulmonary component of the second heart sound and its frequency peak shift toward higher values according to the increase in PA pressure, while the frequency scattering around the peak, expressed by the Q factor, progressively decreases suggesting an increased tension and homogeneity of the vibrating system. Both Fn and the Q factor showed highly significant relations with PA pressure, especially with systolic PA pressure. Considering a multiple regression analysis between PA pressure (systolic, diastolic and mean) on the one hand and Fn and the Q factor on the other, the relations greatly improved with a further decrease of the standard error of the estimate. Figure 2 shows the correlations between the hemodynamic values of systolic (Figure 2a), diastolic (Figure 2b) and mean (Figure 2c) PA pressure and the respective estimated pressures computed from the regression equations. The data suggest the feasibility of a noninvasive estimation of PA pressure from the spectral characteristics of the pulmonary component of the second heart sound. The highest accuracy is obtained for systolic PA pressure; this parameter is therefore the most reliable of the 3 obtained

from the spectral analysis. Systolic PA pressure can be computed from Fn and the Q factor using the following equation: systolic PA pressure = $0.2 \times (\text{Fn}) + 18.9 \times (\text{Q factor}) + 0.3$, with a standard error of the estimate = 4.1 mm Hg which is comparable to the one yielded by the Doppler technique.^{3,5,6}

In conclusion, the modifications of the characteristics of pulmonary component of the second heart sound frequency spectrum (Fn and the Q factor), induced by increased PA pressure, can be used in the clinical setting for the noninvasive estimation of PA pressure in mitral stenosis with the highest degree of accuracy for systolic PA pressure.

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Evolution of the Endocardial Fibrotic Process in Endomyocardial Fibrosis

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The natural history of endomyocardial fibrosis (EMF) has been scarcely studied. Some reports suggest the occurrence of different clinical and histopathologic stages in its evolution, the end stage being characterized by an endomyocardial fibrotic process.¹⁻³ This fibrotic tissue generally involves the ventricular cavity and the papillary muscles, leading to restriction in ventricular filling and to atrioventricular valvular regurgitation associated with severe hemodynamic disturbances, frequently with an ominous prognosis.^{4,5} It is an important cause of restrictive cardiomyopathy in many parts of the world. Whether the fibrosis is simply a static scar tissue, a consequence of an old inflammatory or thrombotic process, or if it has an evolutive character, being actively deposited during the evolution of the disease, is controversial. This study was designed to clarify this point.

We selected 22 of 132 patients (4 male and 18 female patients, aged between 11 and 60 years [mean 38]), with EMF followed-up in our institution. These patients had undergone ≥ 2 cineventriculographies, with intervals varying from 5 to 122 months (mean 47.5). No patient had eosinophilia.

The diagnosis of EMF was based on the angiographic aspect of the ventricles. The main features included changes in ventricular morphology with restriction or obliteration in the inflow tract or apex, leading to reduction in the diastolic ventricular dimension, together with endocardial irregularities. In severe cases the chamber acquires a tubular form due to the almost complete elimination of the inflow tract. Mitral and tricuspid regurgitation were present in almost every examination. Among the 18 patients in the clinical follow-up, 15 were in New York Heart Association functional class I or II and 3 were in class III. The lesion was biventricular in 15, right ventricular in 2 and left ventricular in 1 patient. The other 4 patients were surgically treated, and had 2 comparative examinations performed after resection of the fibrosis and replacement of atrioventricular valves or valvoplasty. All of them were in class III or IV, under-

went surgery of both ventricles, and all had to undergo repeat operation because of biological prosthesis dysfunction. The operations were performed before the description of our new operative technique.⁶ Reoperations were performed 1 to 8 years (mean 4 years and 9 months) after the first operation. Two of the patients who underwent a second operation died within the study period and a necroscopic study was performed in the late postoperative period.

The group of clinically treated patients did not have worsening of fibrosis when the cineventriculograms recorded during the evolution were compared. There was no worsening of the anatomic picture even in patients who had poor functional status (Figure 1).

The group of surgically treated patients did not have new fibrosis formation when the studies performed in the postoperative period were compared. These findings were confirmed by the necroscopic studies performed in the 2 patients who died in the late postoperative period, in whom we did not notice new fibrotic tissue formation. After reoperation, we did not notice return of fibrosis, confirming the observations of many other surgical groups.

There are still several unknown aspects in the development of EMF.¹⁻³ It is probably a dynamic disease, with an initial inflammatory stage, followed by an intracavitary thrombotic process with late fibrosis formation. In the inflammatory or in the necrotic phase, hypereosinophilia and a eosinophilic endomyocarditis are probably the main findings, followed by thrombus deposition in the damaged surface. Subsequently, deposits of fibrosis will

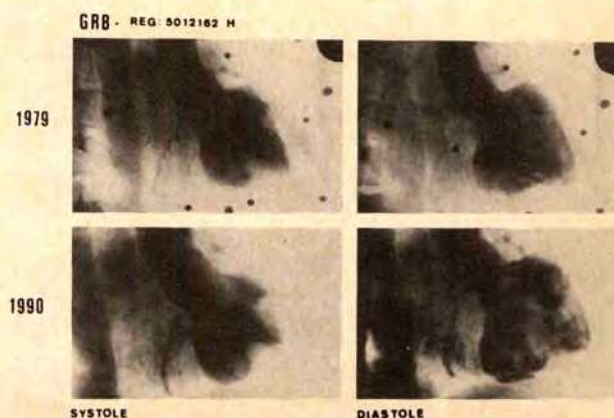


FIGURE 1. Cineventriculograms recorded in 1979 and 1990, in systole and diastole, showing no evolution of the disease.

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appear. This is the most acceptable theory in the pathogenesis of EMF. Death can occur at any stage, and a long survival is followed by fibrous scarring and thickening. Even when it reaches this stage, the disease has a poor prognosis, often in patients in functional class III or IV.^{4,5} So, the usual clinical picture of the disease is characterized by fibrosis as the end stage of a probable eosinophilic heart disease, leading to deformation of the ventricles.

Balakrishnan et al,⁷ in 1986, suggested the possibility of progression or new appearance of angiographic evidence of fibrosis in the unaffected ventricle of 2 patients. This raised the possibility of a slowly progressive disease in a few cases. Lepley et al⁸ thought that new formation of fibrotic tissue would not occur because fibrosis is a scarring process.

Gupta et al,⁹ in 1989, showed angiographic progression of the disease in 8 patients, with repeated cardiac catheterization over a period of 2 to 3 years. They showed progression of the disease in the same ventricle and new involvement of the previously uninvolved ventricle. If the patients are still subjected to the environmental factors responsible for the disease, the recurrence could theoretically occur. Metras et al¹⁰ and Davies et al¹¹ disagree with this point. They noticed no recurrence of the fibrosis despite the persistence of the predisposing factors in their series.

Dubost et al,¹² in 1990, did not observe recurrence of the fibrosis in 6 patients who died in the late postoperative period and in 12 patients who underwent repeat operation because of bioprosthetic dysfunction.

In the last 12 years we examined 142 patients with EMF in our institution. From this group, we selected 22

patients that, in the follow-up, had undergone to ≥ 2 cineventriculographies. In these series, no patient had worsening of the disease.

These results suggest that this stage of EMF is not evolutionary in character, confirming the hypothesis that ventricular fibrosis is only the consequence of a previously healed disease, and not a changing process.

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Incidence of Renal Dysfunction in Adults with Cyanotic Congenital Heart Disease

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Nephropathy has long been recognized as a potential complication of cyanotic congenital heart disease (CHD).¹ Previous studies have demonstrated that glomerular enlargement, mesangial hypercellularity, glomerular capillary congestion and segmental sclerosis occur in some patients with cyanotic CHD.¹ Functional abnormalities including decreased re-

nal plasma flow and glomerular filtration rate, azotemia, abnormal uric acid secretion, proteinuria and nephrotic syndrome also occur in some patients with cyanotic CHD.²⁻⁵ The incidence of renal abnormalities increases with the degree of cyanosis and accompanying erythrocytosis.² Previous studies^{2,3} and our clinical experience suggest that the incidence of renal abnormalities may also increase with increasing duration of cyanosis. Owing to advances in cardiovascular surgery, growing numbers of patients with cyanotic CHD are now surviving longer into adulthood and may be at risk for developing renal abnormalities that may significantly influence their clinical course.⁴ To our knowledge, the incidence of renal

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TABLE I Diagnoses					
	Tetralogy of Fallot (%)	Transposition of Great Arteries (%)	Complex Cyanotic CHD (%)	Eisenmenger Syndrome (%)	Previous CV Surgery (%)
Cyanotic with abnormal UA	9/34 (26)*	6/34 (18)	16/34 (47)*	3/34 (9%)	13/34 (38)*
Cyanotic with normal UA	12/49 (25)*	7/49 (14)	23/49 (47)*	7/49 (14)	24/49 (49)*
Repaired CHD	38/42 (90)	4/42 (10)	0/42 (0)	0/42 (0)	42/42 (100)
*p < 0.05 versus repaired congenital heart disease. CHD = congenital heart disease; CV = cardiovascular; UA = urinalysis.					

TABLE II Abnormalities in Urinalysis in Adults with Repaired and Unrepaired Cyanotic Congenital Heart Disease			
	Patients		p Value
	Cyanotic (%)	Acyanotic (%)	
Proteinuria (≥ 100 mg/dl)	25/83 (30)	0/42 (0)	p < 0.001
Erythrocytes ≥ 3 HPF	9/83 (11)	0/42 (0)	p = 0.027
Leukocytes ≥ 3 HPF	14/83 (17)	4/42 (10)	p = NS
Casts	14/83 (17)	0/42 (0)	p = 0.004
Any of above	34/83 (41)	4/42 (10)	p < 0.001
HPF = high-power field; NS = not significant.			

abnormalities in a clinical population of adult patients with unrepaired cyanotic CHD has not been previously reported.

We retrospectively examined the occurrence of renal function abnormalities in a clinical population of adult patients with cyanotic CHD and erythrocytosis. Patients were selected from the computerized records of the Cardiology Department at Children's Hospital in Boston, Massachusetts, if they were ≥ 21 years of age and treated between 1973 and 1989 for cyanotic CHD with a hematocrit ≥ 55 . A control group of age-matched (≥ 21 years) acyanotic patients with cyanotic CHD repaired ≥ 10 years previously was also examined. All patients in this study had undergone cardiac catheterization with fluoroscopic excretory urogram. All other data were obtained from the hospital medical records.

Parameters of renal function studied included serum creatinine, blood urea nitrogen, and dipstick and microscopic urinalysis obtained in patients after 21 years of age. Urinalyses were obtained routinely before cardiac catheterization and surgery, and during outpatient visits in the emergency department. The most recent result was reported. The previous urinalysis was reported if the most recent was associated with a urinary tract infection (documented by culture) or was accompanied by a significant number of epithelial cells indicating contamination. Proteinuria was defined as $\geq 2+$ protein (≥ 100 mg/dl), hematuria as ≥ 3 red blood cells per high-power field, and pyuria as ≥ 3 white blood cells per high-power field.⁶ Uric acid levels were not routinely measured in asymptomatic patients and were not included in this retrospective study. The medical records were also examined for

other factors that might influence renal function, including congenital urinary tract anomalies, recurrent urinary tract infections, endocarditis-induced glomerulonephritis, systemic hypertension, clinical congestive heart failure and medications. Review of medications was performed with particular attention to current use of any medications (specifically, captopril, furosemide, thiazides, triamterene, sulfonamides, penicillin, phenytoin and allopurinol) and history of aminoglycoside or vancomycin toxicity. The results reported are mean \pm standard deviation. Statistical analysis of the differences among 3 groups was done with a 1-way analysis of variance and, when appropriate, Student-Newman-Keuls test. Comparisons between 2 groups were done with Student's t test. A p value >0.05 was considered significant.

The inclusion criteria were met in 113 cyanotic patients; 83 of these had undergone urinalysis at our institution after their twenty-first birthday and they formed the study group. The control group consisted of 42 "repaired" acyanotic patients who had undergone urinalysis at our institution after their twenty-first birthday. The age distribution of the cyanotic CHD (mean 26, range 21 to 49 years) and control (mean 27, range 21 to 41) patients was similar. Fifty-seven percent of the patients with cyanotic CHD and 48% of the control patients were women (p = not significant). The diagnoses in the cyanotic and control groups are listed in Table I. All control patients with cyanotic heart disease repaired 12 to 24 years earlier had tetralogy of Fallot or transposition of the great arteries. Many patients with cyanotic CHD had more complex cyanotic heart disease (p < 0.05 vs acyanotic patients), although a significant number of patients with cyanotic CHD were in each diagnostic group.

Urinalyses were abnormal in 34 of 83 patients with cyanotic CHD (41%) compared with only 4 of 42 control patients (10%) (p < 0.01) (Table II). Control patients with urinalysis abnormalities were limited to women with isolated pyuria (4 to 18 white blood cells per high-power field). In contrast, proteinuria occurred in 30% of patients with cyanotic CHD, hematuria in 9% and casts in 17% (p < 0.03). Nephrotic syndrome with symptomatic edema developed in 5 of 83 patients with cyanotic CHD (6%) all after age 21 years.

Serum creatinine was elevated to 1.7 ± 2.6 mg/dl in cyanotic patients with abnormal urinalyses compared with 0.8 ± 0.3 mg/dl in those cyanotic patients with normal urinalyses ($p < 0.05$). Three cyanotic patients developed azotemia of sufficient magnitude to require chronic dialysis. One of these patients subsequent to starting hemodialysis had successful surgical repair of tetralogy of Fallot at age 25 years and then underwent renal transplantation. The 2 other patients had nephrotic syndrome and mild azotemia. Immediately after surgical repair at 29 and 36 years of age, respectively, both developed renal failure that required hemodialysis. These 2 patients subsequently died 2 weeks and 2 months, respectively, after surgery.

The cyanotic patients with abnormal urinalyses tended to have a slightly greater hemoglobin (20.6 ± 2.8 g/dl vs 18.6 ± 5.7 g/dl, $p = 0.06$) than those with normal urinalyses. Cyanotic patients with abnormal urinalyses did not differ from those with normal urinalyses in their frequency of acute tubular necrosis, endocarditis, urinary tract infections, congenital urinary tract anomalies, systemic hypertension or congestive heart failure (Table III), or in their chronic use of medications (Table IV). One cyanotic patient developed azotemia and nephrosis following staphylococcus aureus endocarditis and membranous proliferative glomerulonephritis.

This study demonstrates the incidence of renal dysfunction in a relatively large clinical population of young adults with cyanotic CHD. Over one-third of the cyanotic patients (mean age 26 years) have urinary abnormalities suggesting glomerulopathy. This incidence is significantly higher than that in the acyanotic control group with surgically corrected cyanotic CHD, suggesting that the abnormalities are not, as a whole, the result of CHD or its surgical treatment. Cyanotic patients with abnormal urinalyses have a serum creatinine twice as high as those with normal urinalyses; 15% developed nephrotic syndrome and 9% developed renal failure. No other factors, such as urinary tract infections, congenital urologic anomalies, congestive heart failure and nephrotoxic medications, were significantly related to these urinary abnormalities.

A primary limitation of this study is the retrospective design. Although proteinuria, active sediment or nephrotic syndrome occurred in over one-third of young adults in this survey, these abnormalities were not seen in 21 younger children (mean age 6 years) with cyanotic CHD studied by Passwell et al.² In this study, nephrotic syndrome and azotemia were not detected in patients until after age 21 years. Therefore, the risk of glomerulopathy may increase with age. It is possible that as the average age of adults with cyanotic CHD increases, the incidence of acquired renal dysfunction will increase above that seen in this study's relatively young patients.

TABLE III Other Potential Risk Factors for Renal Disease in Patients with Cyanotic Congenital Heart Disease*

	Patients	
	Cyanotic with Normal UA (%)	Cyanotic with Abnormal UA (%)
Urinary tract anomalies	0/49 (0)	1/34 (3)
Recurrent urologic infections	0/49 (0)	0/34 (0)
History of acute tubular necrosis	1/49 (2)	0/34 (0)
History of endocarditis	4/49 (8)	4/33 (12)
Congestive heart failure	21/49 (43)	15/34 (44)
Systemic hypertension ($\geq 145/90$ mm Hg)	2/49 (4)	4/34 (12)
History aminoglycoside toxicity	0/49 (0)	2/34 (6)
Diabetes mellitus	0/49 (0)	0/38 (0)

*All values not significant.
UA = urinalysis.

TABLE IV Chronic Medication Use and Urinalysis Abnormalities in Patients with Cyanotic Congenital Heart Disease*

	Patients	
	With Normal UA (%)	With Abnormal UA (%)
Any medication	29/49 (59)	18/34 (53)
Digoxin	16/49 (33)	7/34 (21)
Furosemide	8/49 (16)	4/34 (12)
Thiazide diuretic	6/49 (12)	3/34 (9)
Spirolactone	5/49 (10)	3/34 (9)
Captopril	0/49 (0%)	0/34 (0)
Penicillin class antibiotics	1/49 (2)	3/34 (9)
Sulfa antibiotic	0/49 (0)	0/34 (0)
Phenytoin	5/49 (10)	4/34 (12)
Allopurinol	1/49 (2)	1/34 (3)

*All values not significant.
Abbreviation as in Table III.

These results indicate a need for a prospective analysis of renal function in adults with chronic cyanosis. The potential for development or progression of renal dysfunction may need to be considered in the timing of surgery in patients with cyanotic CHD.

Because renal dysfunction may occur in patients with cyanotic CHD, and may mimic or complicate the clinical appearance of congestive heart failure and adversely influence pharmacologic and surgical treatment,⁴ renal function should be routinely monitored in these patients. We now obtain urinalyses routinely in our adult patients with cyanotic CHD, and more frequently in those with symptoms of systemic fluid overload. Serum creatinine, blood urea nitrogen and albumin are monitored if the urinalysis is abnormal or the patient is receiving medications that are excreted by the kidneys or are nephrotoxic (e.g., contrast agents).

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Usefulness of Physical Exercise for Maintaining Smoking Cessation in Women

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Successful smoking cessation is a problem for many smokers and the 1-year quit ratio among smokers is <1%.¹ Women may have lower cessation and higher relapse rates than men² and their risk for developing heart disease and lung cancer has increased significantly in recent years.³ Physical activity offers a healthful alternative to smoking: it facilitates regulation of body weight,⁴ moderates mood changes⁵ and improves responses to stress.⁶

We examined the effects of physical exercise on smoking relapse. Twenty healthy women (aged 20 to 50 years) who had smoked ≥ 10 cigarettes each day for at least the past 3 years and had exercised once per week or less for at least the last 6 months were recruited.

Subjects who were in good health and did not take medications or abuse drugs or alcohol, provided informed consent. All women underwent maximal exercise testing on a bicycle ergometer using a protocol that consisted of 2-minute stages with 20-W increments per stage. Subjects exercised to volitional fatigue. Estimated maximal oxygen consumption (VO_2max) was calculated from the maximal work load. Subjects were then randomly assigned to a smoking cessation program alone or to the same program plus cycle ergometer exercise.

The smoking cessation program consisted of eight 1-hour behavior modification sessions over 4 weeks. These were led by the same behavioral psychologist and included sessions on stimulus control, coping with cravings and high risk situations, stress management and relaxation techniques. The psychologist was aware of treatment conditions, but followed the same procedures with each group. Sessions for the 2 groups were conducted separately and the 2 groups had no interaction during the course of the study.

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Subjects were considered to have made a successful 24-hour quit attempt if they reported 24 hours of abstinence and had a carbon monoxide level <8 ppm.⁷ Seven days of abstinence was validated by saliva cotinine, a metabolite of nicotine, of <10 ng/ml⁸ on the last day of smoking cessation treatment. The 1-, 3- and 12-month abstinence rates were also measured by saliva cotinine.

Exercise training consisted of 3 supervised sessions per week for 15 weeks. Each session included 30 to 45 minutes of cycle ergometry at 70 to 85% of the subjects' previously determined maximal heart rate. Subjects were allowed to substitute treadmill walking or rowing for cycle ergometry once per week. Exercise training started 3 weeks before the smoking cessation treatment to allow adaptation to exercise before attempting abstinence. Exercise training continued for the 4 weeks of smoking cessation treatment and for 8 subsequent weeks. The supervising exercise physiologist did not discuss smoking cessation with the subjects. Exercise adherence was assessed by attendance at required exercise sessions.

There were no differences between subjects in the 2 groups at baseline for age, weight, cigarettes smoked per day, estimated VO_2max or expired carbon monoxide (Table I).

All subjects completed the smoking cessation treatment. Seven of the 10 subjects who were in the program of smoking cessation plus exercise complet-

TABLE I Baseline Characteristics

Variable	Smoking Cessation Alone (n = 10)	Smoking Cessation + Exercise (n = 10)
Age (years)	38 \pm 8	40 \pm 9
Cigarettes/day	29 \pm 12	27 \pm 11
Expired carbon monoxide level (ppm)	32 \pm 9	32 \pm 15
Estimated VO_2max (ml/kg/min)	26 \pm 5	26 \pm 6
Weight (kg)	57 \pm 7	62 \pm 15
All values are mean \pm standard deviation. VO_2max = maximal oxygen consumption.		

ed the exercise conditioning protocol. Two subjects who withdrew developed medical problems unrelated to the study and 1 had a scheduling conflict. The remaining 7 subjects who exercised attended 88% of the training sessions. Their mean training heart rate was 80% of maximum. Estimated VO_2max increased significantly with training in subjects who were in the smoking cessation plus exercise program (26 to 31 ml/kg/min) (Table II). Estimated VO_2max did not change in the subjects who underwent smoking cessation alone.

The 24-hour quit rate was 80% for subjects in smoking cessation alone and 70% for those in smoking cessation plus exercise, but only the subjects who exercised maintained their abstinence. The 2 subjects who exercised but ceased training for medical reasons came to all follow-ups and provided smoking data. The remaining subject who withdrew did not attend follow-ups and was counted as a smoker. There was a significant difference in the 7-day abstinence rate at the end of smoking cessation treatment in favor of the exercise group (5 vs 0 subjects). Four of these subjects remained abstinent at 1 month, 3 at 3 months and 2 at 12 months after smoking cessation treatment.

Three studies⁹⁻¹¹ have examined the contribution of physical exercise to smoking cessation. Russell et al,⁹ in the only study of healthy women, found that exercise training did not prevent smoking relapse, but exercising subjects failed to adhere to the training regimen and to achieve physiologic evidence of a training effect. Hill¹⁰ also found that exercise training did not prevent smoking relapse, but this study lasted only 5 weeks and may not have been of sufficient duration to reveal an exercise effect. Taylor et al¹¹ found no difference in the rate of smoking cessation or the frequency of relapse in men who did or did not exercise after a myocardial infarction, but no formal smoking cessation program was provided.

The findings of the present pilot study suggest that exercise training improves quit rates. This study included several methodologic improvements over existing studies including a state-of-the-art smoking cessation program, a supervised exercise program sufficient to produce cardiovascular adaptations, documentation of changes in cardiovascular fitness by exercise testing, and verification of smoking abstinence by salivary cotinine and expired carbon monoxide.

We were surprised that none of the subjects who underwent smoking cessation alone maintained abstinence despite 24-hour quit rates, typical of the literature. Heavy smokers (≥ 25 cigarettes/day) are more likely to be dependent on nicotine and therefore less likely to quit successfully.¹² Also, the quit ratio in the population is lower among women than men.¹² Our subjects were women smoking an average of 28 cigarettes/day and may have had difficulty quitting without adjunctive

TABLE II Body Weight and Estimated VO_2max at Baseline and at 15 Weeks

Variable	Smoking Cessation Alone (n = 10)		Smoking Cessation + Exercise (n = 7)	
	Initial	Change	Initial	Change
Weight (kg)	57 \pm 7	2 \pm 1*	66 \pm 16	0 \pm 2
Estimated VO_2max (ml/kg/min)	26 \pm 5	0 \pm 2	26 \pm 6	5 \pm 3*

*Significant difference ($p \leq 0.01$) within group over time. All values are mean \pm standard deviation. VO_2max = maximal oxygen consumption.

tive treatments, such as physical exercise or a pharmacologic aid.

The "exercise effect" in the present study may be due to more frequent contact among the exercising subjects and with staff. We are examining this possibility by including a standard smoking cessation condition and an "equal contact" condition designed to separate the effects of exercise from the effects of the frequent contact required by supervised training. Nevertheless, these preliminary results suggest that exercise training combined with behavioral smoking cessation treatment is useful in the maintenance of smoking cessation.

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Cardiac Transplant Waiting Lists, Donor Shortage and Retransplantation and Implications for Using Donor Hearts

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Cardiac transplantation is established as the standard therapy for end-stage heart failure.¹ The shortage of donors is the limiting factor in heart transplantation.² Much emphasis has been placed on increasing donor referrals³ and appropriate management of potential donors to widen the donor pool.⁴ An alternative approach is to examine potential cardiac transplant recipients and identify patient subgroups with poor survival. We assessed the impact of donor shortage on the mortality of patients awaiting operation.

Between March 1979 and September 1990 >1,318 patients were referred for assessment for cardiac transplantation at Papworth Hospital in Cambridge. Of these, 776 patients were suitable for formal transplantation assessment. After thorough review, 588 patients were accepted onto the cardiac transplant waiting list, 56 patients were placed onto a provisional list, and the remaining 132 patients were rejected. Our reasons for exclusion in the rejected group were active infection, malignancy (including previously treated disease), raised pulmonary vascular resistance (>4 Wood units), recent pulmonary infarction, extensive cerebrovascular or peripheral vascular disease, active peptic ulceration, psychological or social unsuitability.

Twelve patients have undergone cardiac retransplantation at Papworth Hospital up to September 1990: 1 patient has had a second cardiac retransplant. Therefore a total of 13 grafts (4%) of the series are

retransplants. Nine patients were men and the remaining 3 were women. Five patients received "double" immunosuppressive therapy (cyclosporin and either azathioprine or steroids) and 7 received "triple" therapy (cyclosporin, azathioprine and steroids). The causes of the first graft failure include primary organ failure (1 patient—1 day postoperatively), acute rejection (3 patients—median 11 days postoperatively [range 9 to 41 days]), coronary occlusive disease (8 patients, 9 grafts—median 1,833 days postoperatively [range 191 to 3,232 days]).

The numbers of patients undergoing cardiac retransplantation were too small for extensive risk factor analysis. To detect differences in outcome for various factors, Fisher's exact test was used where appropriate.

Of the group of 588 people on the active waiting list, 399 patients (68%) received their first heart transplant of whom 353 (60%) were men. Treatment varied according to the time of operation. Initially,

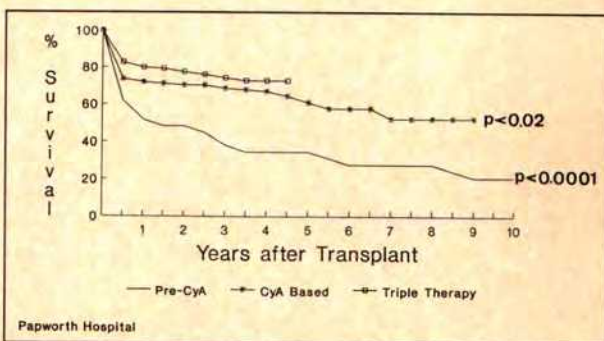


FIGURE 1. Heart transplant patient survival by immunosuppressive group. CyA = cyclosporine A; Pre = before.

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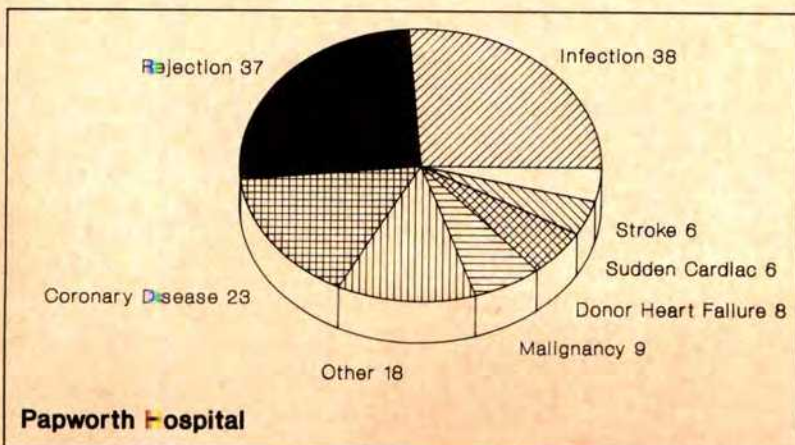


FIGURE 2. Causes of death in 145 patients with cardiac transplants, June 1990.

steroids, azathioprine and antithymocyte globulin were used as immunosuppressive therapy. Cyclosporin A was introduced into the heart transplant program in March 1982 and used in combination with low-dose steroids or azathioprine (double therapy) until April 1986. After this period, all 3 agents were used in combination together (i.e., triple therapy). The actuarial survival has improved with these changes in therapy (Figure 1).

The leading causes of mortality in the early postoperative period (<1 year) are primary organ failure, rejection and infection. As graft failure from these causes becomes less common, coronary occlusive disease becomes the most important late complication (>1 year). All causes of death are shown in Figure 2.

There is no "emergency" category of patients awaiting transplantation at our hospital. However, it is our practice to operate on the sickest patient on the waiting list. Despite this policy, 136 patients (23%) died while awaiting operation. Mean time from acceptance to death was only 66 days.

Eight patients died within a year (67%). This is in contrast to a 1-year mortality of 17% (38 of 221 grafts) in the total group of patients receiving triple immunosuppressive therapy. Seven patients died in the hospital soon after reoperation (median 11 days [range of 0 to 17]). Mean age was 45 years (range 25 to 57), which is similar to a mean age of 44 years (range 6 to 63) for the whole group of transplanted patients.

Three patients developed "late" graft failure, i.e., after discharge from the hospital. One patient died at 93 days from infection, and 1 patient died from acute rejection 2 years after reoperation. Another patient developed severe heart failure due to end-stage coronary occlusive disease after 6 years, and underwent a second retransplant. This patient is currently alive and well 3 years later. The other 2 living patients are alive at 9 months and 4.3 years postoperatively.

It is apparent that without operation a large proportion of patients who are on cardiac transplant waiting lists will die. The critical lack of donor organs has emphasized that the best potential must be realized from each donated organ. It is vital to ensure that appropriate recipients are selected. Not only will the inappropriate recipient die, but a potential suitable recipient will be denied life-saving treatment.

Potential risk factors associated with an adverse outcome are difficult to assess in such a small group of patients. Seven patients underwent operation after formal reassessment for transplantation. All of these patients survived for >1 year and had coronary occlusive disease. The patients surviving for >100 days fall into both of these categories ($p < 0.001$, Fisher's exact test). No patient with infection, rejection or early graft failure survived beyond 93 days.

Other possible risk factors related to poor outcome, which were assessed, included age at retransplantation, serum creatinine before operation, treatment group, preoperative infection, number of rejection episodes, cytomegalovirus status of donor or recipient, original diagnosis or preoperative hypertension. None of these correlated with a poor prognosis, but again the numbers of patients involved are small.

International experience of cardiac retransplantation also suggests that patients who have a cardiac retransplant have a worse outcome with an overall 1-year survival rate of 49% compared with adult patients who have a cardiac transplant for the first time (81%).¹ In addition, patients undergoing surgery within 1 month of the first transplant had particularly poor results, with a 1-year survival of only 37%. In addition, patients undergoing retransplantation for coronary occlusive disease have a higher subsequent incidence of coronary disease than patients having a transplant for the first time.⁵ In combination with our data, this suggests that precious organs should probably be reserved for primary cardiac transplantation.

The high mortality in patients undergoing retransplantation at Papworth Hospital reflects the early attempts to salvage very sick patients with primary organ failure, rejection and infection. As experience has grown and the donor shortage has become critical, the emphasis has shifted away from emergency operations. The long-term complication of heart transplantation is coronary occlusive disease. This disease is often progressive and this allows proper evaluation of all factors involved in reoperating on the individual patient. If there is any role at all for cardiac retransplantation, it lies within this group of patients.

Thus, donor organs are a scarce resource in most branches of human organ transplantation. Without operation a large proportion of patients on cardiac transplant waiting lists die. Cardiac retransplantation is associated with a high postoperative mortality compared with results in patients with a first transplant. Patients who have been formally reassessed for reoperation, i.e., patients with coronary occlusive disease, have a better prognosis than patients who undergo emergency operation.

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Effects of Prednisolone Therapy on Arterial Angiographic Features in Takayasu's Disease

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Patients with Takayasu's disease in the active stage, a time when the inflammatory activity is well reflected by high erythrocyte sedimentation rate, usually respond to corticosteroid therapy.¹⁻⁴ There has been no angiographic evidence of any positive attenuation of the arterial stenoses except in 2 cases.^{5,6} Long-term prednisolone therapy guidelines have also not been documented. I report here the results of a prospective, long-term follow-up study on 118 patients with Takayasu's disease. A comparison of the angiograms obtained at different times in 1 patient was made. Using the life-table method, decrease in the percentage of patients who required prednisolone therapy is estimated. In addition, the method of prednisolone therapy is given attention.

During a 32-year period, from May 1957 to December 1988, 118 Japanese patients with angiography or autopsy-proved Takayasu's disease, or both, were examined, treated and prospectively followed up for 11 ± 7 years (mean \pm standard deviation) after the diagnosis. The present report concerns these 118 patients (9 men and 109 women). The average age at the

time of the diagnosis and the onset of symptoms and signs was mean \pm standard deviation 30 ± 11 years (range 8 to 64) and 23 ± 8 years, respectively. There were 14 patients followed angiographically.

Concerning the disease activity, a persistent erythrocyte sedimentation rate of ≥ 20 mm/hour Westergren was considered to indicate the inflammatory active stage of the disease and one < 20 mm/hour the inactive stage.⁷ At the diagnosis, there were 90 (76%) with active disease and 28 (24%) with inactive disease. Active patients were selected for oral prednisolone; 12 did not receive it, 9 became inactive and 3 remained active during the follow-up period. Among the 78 active patients with prednisolone therapy, complete withdrawal of prednisolone was feasible for 20 patients, 39 were still taking prednisolone therapy as of December 1988 and the remaining 19 had an interrupted prednisolone therapy. The initial daily dose of prednisolone prescribed was usually 30 to 50 mg; this dose was gradually reduced to the first maintenance dose, usually 15 to 25 mg (rarely 30 mg), up to the end of the first month of initiation of treatment. A maintenance dose was usually continued for at least 3 to 6 months, often 12 months or longer. Further adjustment of the daily dose after the first prescribed main-

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TABLE 1 Angiographic Follow-Up of 14 Women with Takayasu's Disease

Pt. No.	Age (yr)		Interval (yr)	Prednisolone (mg/day)		ESR (mm/hour)		Angiographic Changes in Arteries*									
	Onset	First Angio-graphy		At Initiation	At 2nd Angio-graphy	Before Steroid Therapy	At 2nd Angio-graphy	Angiographic Changes in Arteries*									
								Aorta	BCT	CCA	CT	FA	RA	SA	SMA	VA	
Prednisolone Therapy: Nine Active Patients																	
93	8	8	8	9.7	60	11.25	121	5	↓	—	—	—	x	↓L	—	↓	
97	16	21	17	5.1 [†]	50	13.75 [§]	142	8 [§]	—	—	↓L	—	↑L	—	—	—	
104	18	34	35	2.8	50	3.75	84	10	—	↓	↓L, R	—	x	—	—	—	
105	17	22	22	1.5	30	15.00	50	8	—	—	—	—	x	—	↓R	—	
107	44	44	44	0.7	50	22.50	70	4	—	—	—	—	x	—	—	—	
108	16	17	17	1.7	50	17.50	60	16	—	↓	↓R	—	x	—	↓L, R	—	
109	16	18	18	3.7	20	16.25	107	10	↓LIR	↓LIR	↓LIR	—	x	↓L, R	↓L	—	
					(50)												
112	17	18	18	2.7	40	25.00	152	8	—	—	—	↑	x	↓L	—	—	
113	22	23	32	11.6 [†]	50	1.25 [§]	102	8 [§]	—	—	—	—	x	↓L	—	—	
Prednisolone Therapy (none or interrupted): Four Active and One Inactive Patient																	
17	17	17	—	1.0	0	0	32	29	↑	—	—	—	x	—	—	—	
45	23	23	28	3.3	20	Interrupted	105	25	—	—	↑R	—	x	—	↑R	—	
54	22	24	—	3.0	0	0	12	12	↑LIR	—	—	—	x	—	—	↑L	
66	34	33	38	1.8	30	Interrupted	35	42	—	—	↑R	—	x	—	—	—	
103	9	10	—	18.1	0	0	83	8	—	—	—	—	x	↓L	—	—	
*For evaluation of angiographic findings, a decrease and increase in the degree of luminal diameter stenosis by ≥ 25% was defined as angiographic improvement and progression, respectively; [†] Second angiography; [‡] Second to third angiography; [§] Third angiography. Data on case 104 were reported. ⁶ BCT = brachiocephalic trunk; CCA = common carotid artery; CT = celiac trunk; ESR = erythrocyte sedimentation rate, Westergren; FA = femoral artery; L = left; LIR = luminal irregularity; R = right; RA = renal artery; SA = subclavian artery; SMA = superior mesenteric artery; VA = vertebral artery; ↓ = improvement; ↑ = progression; — = unchanged; x = no femoral arteriography; () = prednisolone dose increased 2 months after the initiation.																	

*For evaluation of angiographic findings, a decrease and increase in the degree of luminal diameter stenosis by $\geq 25\%$ was defined as angiographic improvement and progression, respectively; †Second angiography; ‡Second to third angiography; §Third angiography. Data on case 104 were reported.⁶
BCT = brachiocephalic trunk; CCA = common carotid artery; CT = celiac trunk; ESR = erythrocyte sedimentation rate, Westergren; FA = femoral artery; L = left; LIR = luminal irregularity; R = right; RA = renal artery; SA = subclavian artery; SMA = superior mesenteric artery; VA = vertebral artery; ↓ = improvement; ↑ = progression; — = unchanged; x = no femoral arteriography; () = prednisolone dose increased 2 months after the initiation.

tenance dose was usually made by a 5 to 10% reduction of the preceding maintenance dose. The effects of prednisolone withdrawal were usually monitored by a persistent erythrocyte sedimentation rate value of <20 mm/hour. The cumulative percentage of patients who required prednisolone therapy was estimated using the life-table method.⁸ The complete withdrawal of prednisolone associated with a persistent erythro-

cyte sedimentation rate of <20 mm/hour was used as the end point.

Of the 14 patients followed angiographically, Table I compares the effects of prednisolone therapy in the 9 active patients with the remaining 5 who had no or an interrupted prednisolone therapy. In the former 9, all but 1 patient (case 107) with no significant improvement showed angiographic evidence of improvement in the involved arteries, including 2 (cases 97 and 112) with partial progression. Angiograms are shown of case 109 (Figures 1 and 2), 108 (Figure 3) and 93 (Figure 4). Among the latter 5 (Table I), 3 active patients with no or an interrupted prednisolone therapy and 1 inactive patient showed angiographic evidence of progression, and the final active 1 was improved and became inactive, even with no ingestion of prednisolone.

Figure 5 shows the average daily dose of prednisolone and the average erythrocyte sedimentation rate

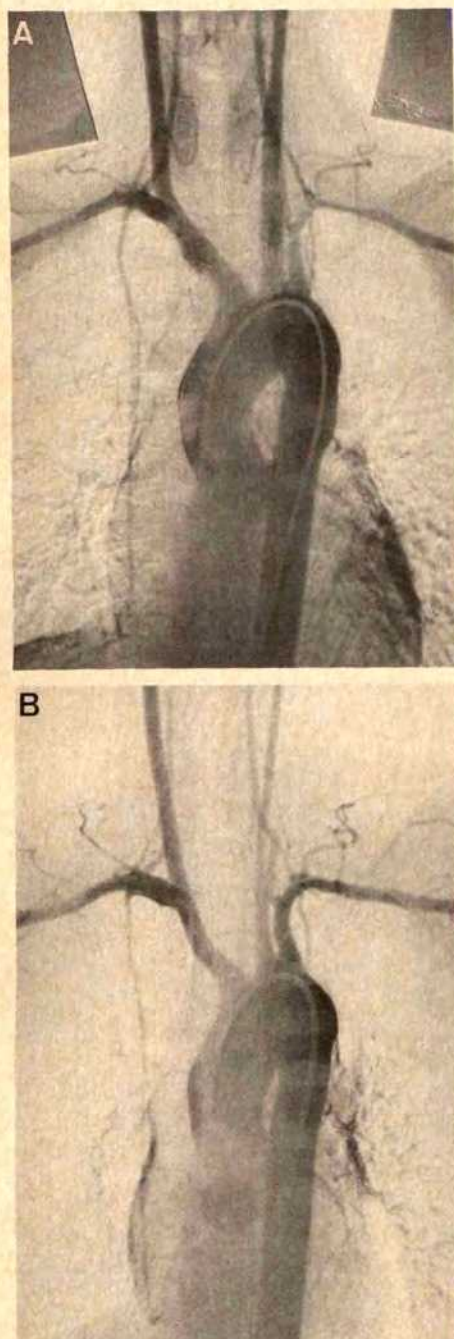


FIGURE 1. Thoracic aortograms (subtraction) in patient 109. **A**, at age 18 years, 7.4 weeks with prednisolone therapy, there is a stenosis of the left midsubclavian artery, and luminal irregularities of the left common carotid, brachiocephalic trunk and upper thoracic aorta. **B**, at age 22 years, 3.8 years after therapy, there is regression of the narrowing and disappearance of the luminal irregularities.

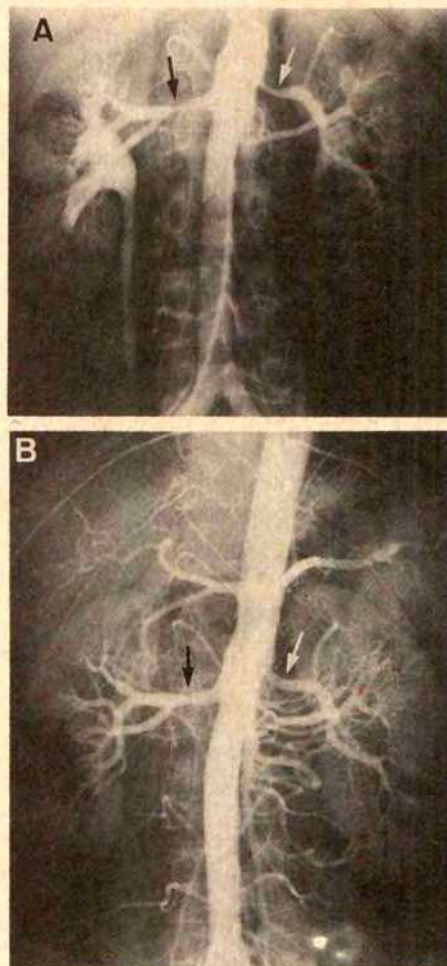


FIGURE 2. Abdominal aortograms (**A** and **B**) in patient 109 recorded at the same time as thoracic aortograms (Figure 1, **A** and **B**), respectively. **A**, there is stenoses of bilateral renal arteries (black and white arrows, right and left renal arteries, respectively) and luminal irregularity of the upper abdominal aorta. **B**, there is marked improvement (black and white arrows, right and left renal arteries, respectively) of the stenoses and slight improvement of the luminal irregularity.

value at yearly intervals during 1 month to 12 years in 59 patients in the active stage. The high erythrocyte sedimentation rate (average 89 ± 37 mm/hour) before prednisolone therapy was rapidly and markedly improved (average 26 ± 19 mm/hour) within the first month of initiation. The average initial daily dose was 37 ± 13 mg. Of the 59 patients, 20 completed prednisolone therapy during the average period of 9 ± 3 years (range 4 to 19). In these 20, there was no flare-up of the disease activity during the average interval of 2.9 ± 2.1 years from the complete withdrawal of prednisolone to December 1988. In the 78 active patients receiving prednisolone therapy, including 19 receiving an interrupted prednisolone therapy, the 12-year percent of patients who required prednisolone therapy after initiation was mean \pm standard error of the mean $53 \pm 9\%$.

The present series shows that in 8 patients with active Takayasu's disease, adequate, long-term prednisolone therapy plays a major role in obvious angiographic improvement of arterial lesions because of the rare occurrence of spontaneous improvement of the involved arteries. There appears to be documentation on only 2 cases of spontaneous regression of stenosis, including case 103 reported here and 1 reported elsewhere.⁹ The inactive one (case 54) was asymptomatic but progression was

evident on the angiograms. The sites of progression were probably in the subclinical, active stage, as described elsewhere.¹⁰

To prevent frequent flare-ups of high erythrocyte sedimentation rate, with or without symptoms during the

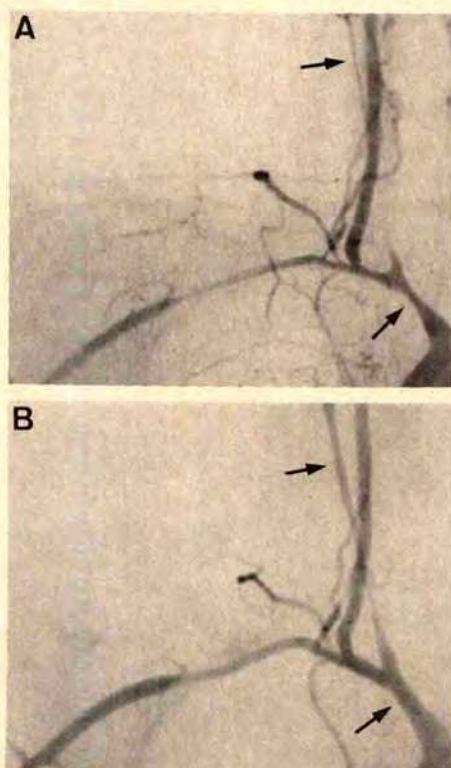


FIGURE 3. Aortic arch aortogram (subtraction) in patient 108. **A**, at age 17 years, 12 weeks with prednisolone therapy, there is severe stenoses of the right common carotid (upper arrow), the brachiocephalic trunk (lower arrow) and the right subclavian artery. **B**, at age 18 years, 1.9 years after therapy, there is a marked or moderate improvement of stenoses of these vessels.

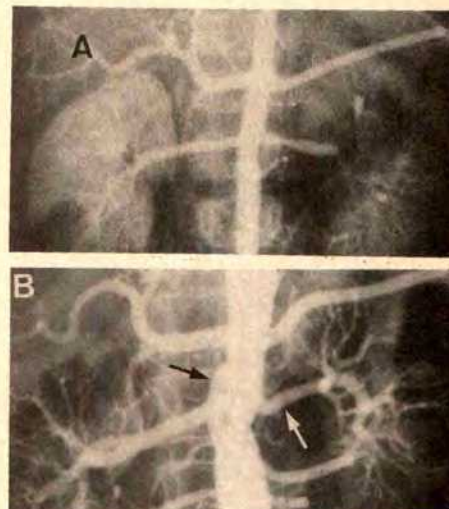


FIGURE 4. Abdominal aortogram in patient 93. **A**, at age 9 years, 32 weeks with prednisolone therapy, note stenosis of the left renal artery, no evidence of the superior mesenteric artery and stenosis of the thoracoabdominal aorta. **B**, at age 18 years, 10.3 years after therapy, there is a regression of stenosis of the left renal artery (white arrow), appearance of the superior mesenteric artery (black arrow) and regression of the aortic narrowing, except for an unchanged stenosis of the aortic short segment in the vicinity of the renal arterial orifices.

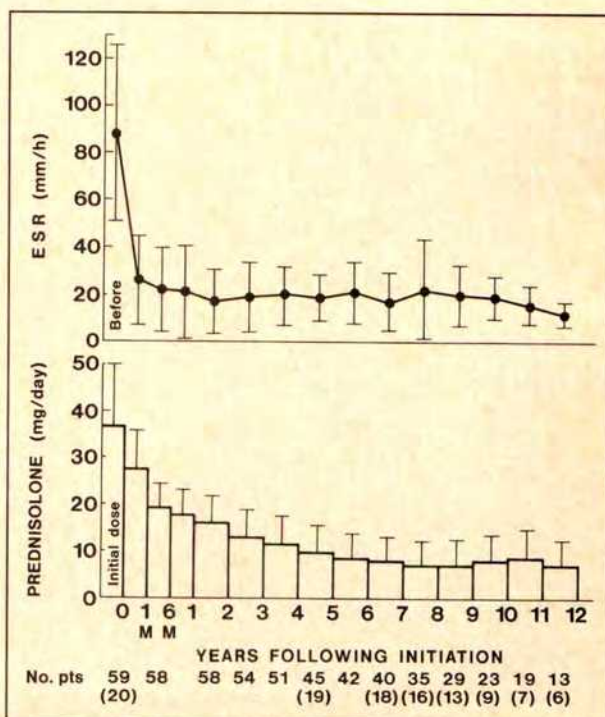


FIGURE 5. Prednisolone treatment regimen and erythrocyte sedimentation rate (ESR) during 1 month to 12 years of follow-up in 59 patients with active Takayasu's disease. Numbers in parentheses indicate those who completed prednisolone therapy. Mean values \pm standard deviation are shown.

tapering off of prednisolone, the following is important: (1) continuation of the first maintenance dose for at least 3 to 6 months; (2) care not to make too rapid a reduction in the dose of prednisolone, particularly during the first 2 or 3 years from the initiation, to reach 15 mg/day; and (3) very gradual tapering from the maintenance dose of 5 or 7.5 mg/day in the late period of prednisolone therapy. When the erythrocyte sedimentation rate is persistently ≤ 10 mm/hour during 3 to 6 months on a maintenance dose of prednisolone, a small reduction in dose is usually feasible.

This prospective follow-up of 118 patients with Takayasu's disease for 11 ± 7 years revealed that dramatic improvement often occurs in patients receiving adequate prednisolone therapy. For most such patients, a prolonged prednisolone therapy is needed to control the disease activity, reflected by high erythrocyte sedimentation rate, before a complete withdrawal of prednisolone can be considered. This study also provides a guideline for long-term prednisolone therapy for patients with active Takayasu's disease.

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Noninvasive Estimation of Left Ventricular Contractile State and Afterload in Normal Newborn Infants

Hiroshi Igarashi, MD, Hirohiko Shiraishi, MD, Hideki Endoh, MD, and Masayoshi Yanagisawa, MD

Cardiac performance is altered by loading conditions and by heart rate, especially in newborn infants. Ejection phase indexes such as ejection fraction and fractional shortening might be useful in evaluating their cardiac function. The clinical use of these indexes is limited by the inability to distinguish between the effects of altered loading conditions and of abnormalities in left ventricular contractility. The relation between end-systolic endocardial meridional stress and the rate-corrected velocity of circumferential fiber shortening is a sensitive echocardiographic method for evaluating left ventricular contractility, which is relatively independent of loading.¹⁻⁵ There have been no reports on the relation between endocardial meridional stress and rate-corrected velocity of circumferential fiber shortening in newborns. We studied the relation between endocardial meridional stress and the rate-corrected velocity of circumferential fiber shortening in normal newborn infants to determine the normal values and to estimate the contractile state.

We evaluated 26 normal full-term infants, aged 65 to 90 hours. There were 11 male and 15 female in-

fants, none of whom had cardiovascular symptoms or signs and were confirmed to have no congenital heart disease including patent ductus arteriosus by 2-dimensional echocardiography and color flow imaging (SSH-65A, 5-MHz transducer, Toshiba, Tokyo). We obtained all the measurements while the infants were asleep without sedatives. First, to evaluate the circularity of the left ventricle, we measured the internal diameter along the anteroposterior axis and that along the transverse axis at the papillary muscle level in the short-axis view by 2-dimensional echocardiography.⁶ We compared these 2 diameters using a paired *t* test and considered a *p* value < 0.05 as statistically significant. Hard copies were made of the simultaneous recordings of the M-mode echocardiogram of the left ventricle at the tips of the mitral valve leaflets, electrocardiogram, phonocardiogram and indirect carotid pulse tracing with a paper speed of 100 mm/s. We also obtained systolic and diastolic blood pressure simultaneously. Left ventricular internal dimension and posterior wall thickness were measured at end-systole and end-diastole in 5 consecutive beats. Left ventricular ejection time was calculated from the carotid pulse tracing and rate-corrected to a heart rate of 60 beats/min by dividing by the square

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TABLE I Means \pm Standard Deviations (SD) and Ranges of Clinical Data: Indexes of Systolic Function and Wall Stress in 26 Normal Infants

	Mean \pm SD	Range
Age (hours)	78 \pm 6	65 to 90
Weight (g)	3,086 \pm 444	2,370 to 4,190
Body surface area (m ²)	0.20 \pm 0.02	0.18 to 0.23
Rate-corrected VCF (circ/s)	0.87 \pm 0.18	0.57 to 1.22
Fractional shortening	0.24 \pm 0.05	0.16 to 0.34
Endocardial meridional stress (g/cm ²)	53.5 \pm 11.3	33.2 to 71.1

VCF = velocity of circumferential fiber shortening.

root of the PR interval. The end-systolic pressure was estimated by assigning the noninvasively obtained peak systolic pressure to the peak and end-diastolic pressure to the nadir of the carotid pulse with subsequent linear interpolation to the level of the incisura. From these data we calculated the rate-corrected velocity of circumferential fiber shortening, fractional shortening and endocardial meridional stress. The latter was calculated by the method of Grossman et

al¹ (Table I). Linear regression analysis was used to determine the significance of the correlations between the rate-corrected velocity of circumferential fiber shortening or fractional shortening and endocardial meridional stress.

Left ventricular shape was found to be circular in our study; the anteroposterior diameter of the left ventricle (11 ± 1 mm) was not significantly different from the transverse diameter (11 ± 1 mm) in systole. The relation between endocardial meridional stress and the rate-corrected velocity of circumferential fiber shortening in normal newborns is shown in Figure 1, and that between endocardial meridional stress and fractional shortening is shown in Figure 2. There was an inverse linear correlation between endocardial meridional stress and the rate-corrected velocity of circumferential fiber shortening ($r = -0.48$, velocity of circumferential fiber shortening = -0.0075 end-systolic endocardial meridional stress + 1.27, $p < 0.05$) and between endocardial meridional stress and frac-

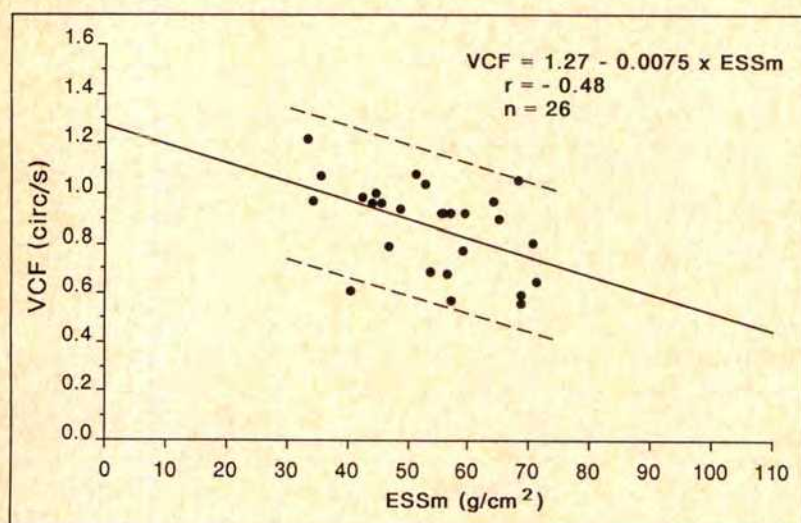


FIGURE 1. Relation of endocardial end-systolic meridional stress (ESSm) to rate-corrected velocity of circumferential fiber shortening (VCF) in 26 subjects. The linear regression equation is given and illustrated along with 95% confidence intervals (dashed lines), correlation coefficient (r) and the number of subjects (n).

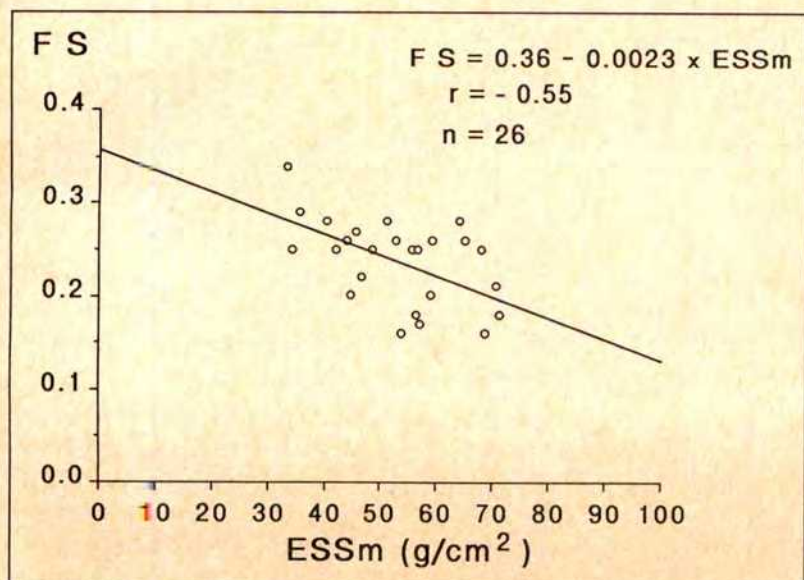


FIGURE 2. Relation of endocardial end-systolic meridional stress (ESSm) to fractional shortening (FS) in 26 subjects. The linear regression equation is given and illustrated along with 95% confidence intervals, correlation coefficient (r) and the number of subjects (n).

tional shortening ($r = -0.55$, fractional shortening = -0.0023 end-systolic endocardial meridional stress + 0.36 , $p < 0.05$). Inverse correlation between endocardial meridional stress and the rate-corrected velocity of circumferential fiber shortening in newborn infants was in agreement with the observations made by Colan² and Franklin³ and their co-workers in older infants and children. We therefore consider this relation to be applied to all pediatric age ranges. The values of endocardial meridional stress in our study were higher than those reported for older infants. This might be explained by the elevated afterload due to loss of the placental circulation and the change in environmental temperature.

These normal values can provide an accurate estimation of the left ventricular contractile state of newborn infants.

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Transesophageal Echocardiographic Characterization of Pulmonary Vein Flow Not Due to Atrial Contraction or Mitral Regurgitation

Tomasz J. Pasierski, MD, Mary A. Alton, MD, and Anthony C. Pearson, MD

In normal human subjects who are in normal sinus rhythm, transthoracic echocardiographic studies have demonstrated that blood flows from the pulmonary veins into the left atrium during both systole and diastole.¹ Using transesophageal echocardiography, we have demonstrated that a brief period of flow reversal characterized by retrograde left atrial to pulmonary vein flow is seen in most normal subjects during left atrial contraction.² Recent studies have demonstrated the importance of recognition of pulmonary vein flow reversal occurring during systole as a marker of severe mitral regurgitation.³ In patients in atrial fibrillation, however, we have noted pulmonary vein flow reversal which appears systolic in timing in the absence of significant mitral regurgitation. The current study characterizes this nonatrial flow reversal and compares its flow characteristics with the flow reversal noted in sinus rhythm.

Left upper pulmonary venous flow was recorded during transesophageal study in 12 subjects with normal sinus rhythm and in 9 subjects with atrial fibrillation. Clinical data of examined subjects are given in Table I. Transesophageal echocardiography was performed after topical anesthesia of the hypopharynx with 10% cetacaine and intravenous sedation with midazolam and/or meperidine. A 5.0-MHz transducer mounted on the tip of a modified flexible gastroscope

(Hewlett-Packard 77020 Sonos 500 and Sonos 1000) was introduced to a depth of 25 to 30 cm. The left upper pulmonary vein was identified with the aid of color-flow imaging. The pulsed wave Doppler sample volume (3 mm in length) was placed in the left upper pulmonary vein an average 0.5 to 1 cm from its orifice. Mitral inflow was recorded using pulsed wave Doppler with the sample volume located between the tips of the mitral leaflets. An electrocardiographic II lead was recorded simultaneously. All Doppler recordings were printed on a strip-chart recorder at a speed of 100 mm/s for further off-line analysis.

During each cardiac cycle, forward systolic flow, forward diastolic flow and flow reversal were identi-

TABLE I Clinical Characteristics of Patients in Sinus Rhythm and with Atrial Fibrillation

	Normal Sinus Rhythm	Atrial Fibrillation
Age (years)	46 ± 7	66 ± 6*
Number	12	9
Heart rate	71 ± 16	84 ± 13
Ejection fraction	63 ± 5	59 ± 13
No MR	4	4
1 + MR	3	3
2 + MR	2	1
3 + MR	1	0
4 + MR	2	1
Clinical diagnosis	4 CSE, 2 BE, 2 MVD, 2 AD, 1 SM, 1 MP	5 CSE 3 MP, 1 MVD

* $p < 0.05$ versus normal sinus rhythm.
AD = aortic dissection; BE = bacterial endocarditis; CSE = cardiac source of embolism; MR = mitral regurgitation; MP = prosthetic mitral valve; MVD = mitral valve disease; SM = subaortic membrane.

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TABLE II Pulmonary Venous Flow Characteristic of Patients in Sinus Rhythm and in Atrial Fibrillation

	Normal Sinus Rhythm	Atrial Fibrillation
No. of patients	12	9
Pulmonary venous flow reversal		
Early	11	0
Late	3	6
Time from P wave to onset of early pulmonary venous flow reversal (ms)	97 ± 30	—
Time from P wave to onset of mitral late inflow (ms)	84 ± 23	—
Time from QRS onset wave to onset of pulmonary venous flow reversal (ms)	—	72 ± 22
Time from QRS onset to the end of mitral inflow (ms)	—	67 ± 26
Pulmonary venous flow reversal velocity (cm/s)	22 ± 6	22 ± 8
Pulmonary venous flow reversal integral (cm)	1.9 ± 1.0	1.4 ± 0.4
Pulmonary venous flow reversal/forward flow ratio (%)	12 ± 8	13 ± 8

found in pulmonary venous velocity tracings and the velocity, duration and flow-velocity integral calculated. Intervals from onset of P wave and from onset of Q wave to beginning of pulmonary venous reversal were calculated (Figure 1). Mitral inflow tracings were used to calculate the interval between the P wave of the electrocardiogram and the beginning of mitral inflow caused by atrial systole and the interval between the beginning of the QRS and the end of mitral inflow. The interobserver linear regression standard error of estimate was ≤ 6 ms for all measurements. The values were averaged from 5 cardiac cycles for patients in sinus rhythm and 6 to 8 cycles for patients

with atrial fibrillation. The severity of mitral regurgitation was graded from 1 to 4+ based on maximal color flow jet area.³ An unpaired Student's t test was used to compare continuous variables in the 2 groups. Pearson's correlation coefficients were calculated. A p value <0.05 was considered statistically significant. All values are given as a mean \pm standard deviation.

Two types of reversal of pulmonary venous flow were identified (Table II). The first pattern, designated "early reversal," always occurred before the QRS with an onset averaging 97 ± 30 ms after the onset of the electrocardiographic P wave. The reversal lasted 99 ± 36 ms (mean velocity 22 ± 6 cm/s) (Figure 2). The early reversal pattern was found in 11 of 12 subjects (91%) in normal sinus rhythm but in none of the patients with atrial fibrillation. The time from P wave to onset of the early reversal valve correlated ($r = 0.97$) with the time from P wave to onset of forward mitral atrial systolic flow (Figure 3).

The second pattern, termed "late reversal," always followed the QRS, with an onset averaging 72 ± 22 ms after the beginning of the QRS (Figure 4). The reversal lasted 88 ± 22 ms (mean velocity 22 ± 8 cm/s). Late reversal was found in 6 of 9 subjects (66%) with atrial fibrillation, none of whom had significant mitral regurgitation. In 3 subjects with normal sinus rhythm both early and late reversal patterns were noted (Figure 5). The time from Q-wave to onset of late reversal of pulmonary venous flow correlated with the time from Q wave to end of mitral inflow ($r = 0.85$) (Figure 6). There was no significant difference in peak velocity, flow-velocity integral, flow duration or flow reversal/forward flow ratio between early and late reversal patterns.

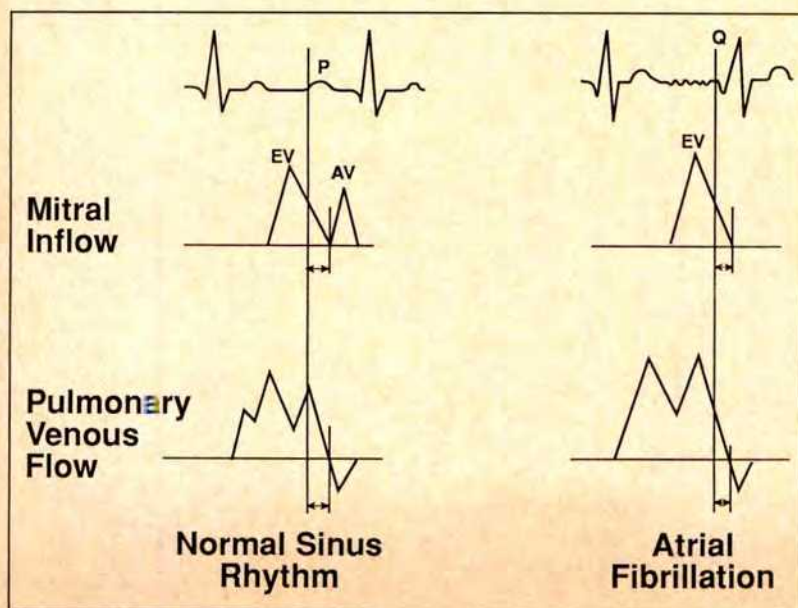


FIGURE 1. Schematic presentation of evaluated time intervals. **Left bottom,** onset of P wave to beginning of pulmonary venous reversal; **left top,** onset of P wave to onset of A wave of mitral inflow; **right bottom,** onset of Q wave to beginning of pulmonary venous reversal; **right top,** onset of Q wave to end of mitral inflow. AV = late mitral inflow; EV = early mitral inflow.

Pulmonary venous flow reversal in subjects with preserved left atrial contraction was previously described by Smallhorn et al.⁴ On the other hand Keren et al.¹ did not find atrial reversal in any of 18 subjects in whom right upper pulmonary venous flow was analyzed with surface

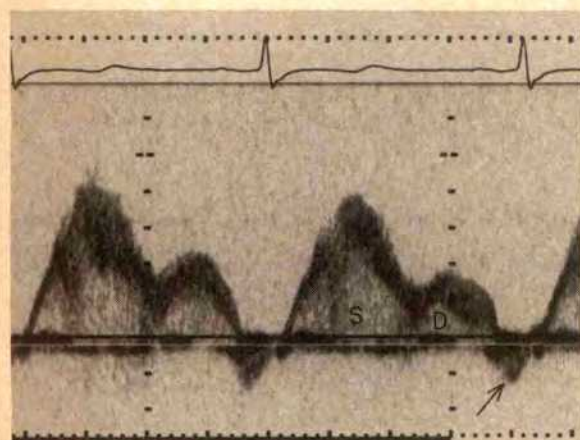


FIGURE 2. Early pulmonary venous flow reversal in patient in normal sinus rhythm. Arrow, pulmonary venous flow reversal. D = diastolic flow; S = systolic flow.

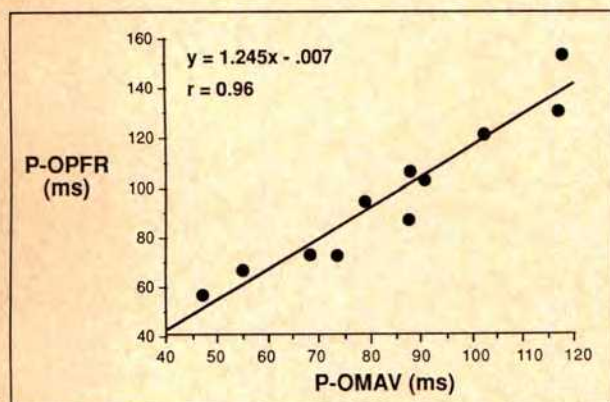


FIGURE 3. Relation between the time from electrocardiographic P wave to Doppler onset of pulmonary flow reversal (P-OPFR), and the time from electrocardiographic P wave to Doppler onset of late mitral inflow (P-OMAV).

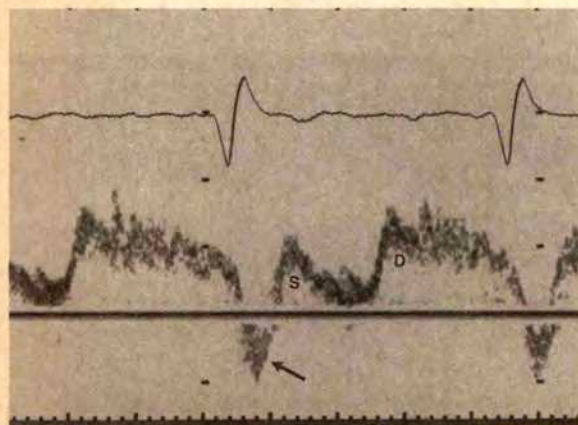


FIGURE 4. Late pulmonary venous flow reversal in patient in atrial fibrillation. Arrow, pulmonary venous flow reversal. D = diastolic flow; S = systolic flow.

echocardiography. The presence of pulmonary venous flow reversal after atrial systole can be explained by regurgitation of blood into the pulmonary veins due to transient reversal of the gradient between the pulmonary veins and left atrium during left atrial contraction. This regurgitation does not seem to be hemodynamically important, as shown by the low reverse to forward flow ratio ($12 \pm 8\%$).

Flow reversal in pulmonary veins in patients with atrial fibrillation not related to mitral regurgitation has not been previously described. This "non-atrial" flow reversal is very similar in magnitude and duration to "atrial" flow reversal in patients with sinus rhythm. However, the timing of the later reversal is clearly different beginning an average 80 ms after the Q wave. Because the onset of this flow is so closely related to the end of mitral flow, a causal relation is suggested. Late reversal may be explained by a transient reversal of the left atrial-pulmonary venous gradient due to transfer of blood contained within the mitral valve during ventricular systole into the left atrium. Meissner et al.⁵ using electromagnetic flow probes, measured a transient period

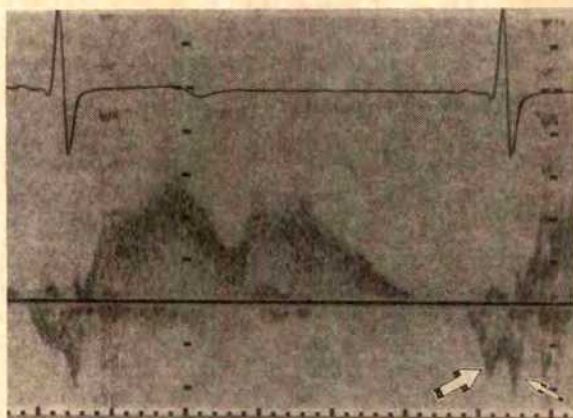


FIGURE 5. Double reversal in patient with sinus rhythm (thick arrow, early reversal; thin arrow, late reversal).

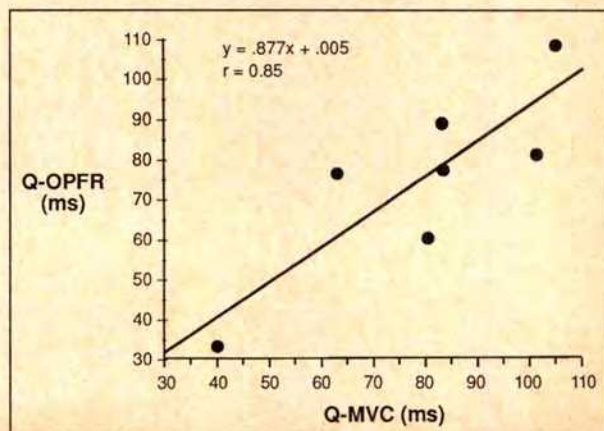


FIGURE 6. Relation between the time from onset of QRS to Doppler onset of pulmonary flow reversal (Q-OPFR) and the time from onset of QRS to Doppler end of mitral inflow (Q-MVC).

of flow reversal at the level of the mitral anulus at onset of ventricular systole in dogs. Mitral leaflets before ventricular systole are almost closed in patients with preserved atrial function but they remain in a semi-open position in patients without atrial mechanical activity, i.e., atrial fibrillation.⁶

It is important to recognize that late reversal pattern represents a normal variant in patients in atrial fibrillation and does not imply the presence of significant mitral regurgitation. Systolic flow reversal due to severe mitral regurgitation occurs during the latter two-thirds of systole as left atrial pressures increase.³ In contrast, the late reversal we have identified begins in the first 120 ms after the onset of the QRS and immediately after mitral closure. In the current study, left atrial venous backflow occurring just after the QRS was also found in 3 patients in sinus rhythm with short PQ intervals. In these subjects, the mitral valve might not have been closed when ventricular systole occurred. Interestingly, the magnitude of regurgitation is the same for patients with early and late regurgitation.

In conclusion, 2 different patterns of pulmonary venous flow reversal not related to mitral regurgitation have been described. Although the hemodynamic significance of this reflux appears to be negligible, increased understanding of atrial mechanics may be gained by further study.

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Dilution of Potent Drugs

Michel Millereau, MD

Many potent drugs prescribed with a precise dosage require the use of an automatic syringe. There are many ways, often aided by an abacus, to compute the patient's weight, the dosage in $\mu\text{g}/\text{kg}$ and drug dilution. We report a convenient dilution method currently used in our hospital designed for any drug through which a $1\text{-}\mu\text{g}/\text{kg}/\text{min}$ dosage is obtained with 1 ml/hour.

An amount of drug equal to 3 times the body's weight (in kg) is diluted to 50 ml with water: $3 \times \text{body weight (kg)} = \text{drug amount (mg) in 50 ml}$. This implies $1 \text{ ml/hour} = 1 \mu\text{g}/\text{kg}/\text{min}$.

Example 1: dobutamine for a 50-kg patient — $50 \times 3 = 150 \text{ mg in 50 ml}$. This implies $1 \text{ ml/hour} = 1 \mu\text{g}/\text{kg}/\text{min}$.

When a dosage of $0.1 \mu\text{g}/\text{kg}/\text{min}$ is desirable in the case of more potent drugs, a simple 10-fold dilution of the drug is necessary: $0.3 \times \text{body weight (kg)} = \text{drug amount (mg) in 50 ml}$. This implies $1 \text{ ml/hour} = 0.1 \mu\text{g}/\text{kg}/\text{min}$.

Example 2: norepinephrine for a 80-kg patient — $80 \times 0.3 = 24 \text{ mg in 50 ml}$. This implies $1 \text{ ml/hour} = 0.1 \mu\text{g}/\text{kg}/\text{min}$. With a speed range between 2.5 and 30 ml/hour, resulting outflow varies from 0.25 to $3 \mu\text{g}/\text{kg}/\text{min}$.

For epinephrine that requires a smaller dosage, an extra 10-fold dilution is applied: $0.03 \times \text{body weight (kg)} = \text{drug amount (mg) in 50 ml}$. This implies $1 \text{ ml/hour} = 0.01 \mu\text{g}/\text{kg}/\text{min}$.

Example 3: epinephrine for a 67-kg patient — $67 \times 0.03 = 2 \text{ mg in 50 ml}$. This implies $1 \text{ ml/hour} = 0.01 \mu\text{g}/\text{kg}/\text{min}$.

This dilution offers a safe and convenient method that is quickly effective in emergency situations without use of an abacus or calculator.

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Abstracts

American Academy of Pediatrics
Section on Cardiology
33rd Annual Meeting
New Orleans, Louisiana
October 25-27, 1991

The following abstracts were selected for presentation in a peer-review process by the Executive Committee of the Section on Cardiology, American Academy of Pediatrics. The first 6 abstracts were selected as finalists in the Young Investigator Award Competition.

Abstracts 1 through 20 will be presented on Saturday, October 26, and abstracts 21 through 38 on Sunday, October 27.

1

VIMENTIN mRNA LOCATION IN MUSCLES CHANGES DURING DEVELOPMENT

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The mRNAs for some cytoskeletal proteins are localized, suggesting that mRNA for cytoskeletal proteins may concentrate at sites appropriate for assembly. To test this hypothesis, we observed vimentin mRNA in developing chicken muscle cultures by *in situ* hybridization with a digoxigenin labeled DNA probe to vimentin, detected by confocal microscopy using fluorescent anti-digoxigenin antibody. This method has submicron resolution. In developing muscle, vimentin mRNA was bipolar in young myoblasts, somewhat perinuclear in elongated myoblasts and spread fibroblasts, and diffuse in young and developing myotubes. In mature myotubes, vimentin mRNA occurs at costameres with vimentin protein. Localization of mRNA may prove as important for assembling and maintaining differentiated cytoskeletal as it is for organizing the embryo.

2

SINGLE CHANNEL RECORDING OF CALCIUM CURRENT IN NEONATAL RABBIT VENTRICULAR MYOCYTES

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Previous whole cell recordings have shown that Ca^{2+} current density in immature ventricular myocytes is smaller than in adult cells. However, little is known about the properties of single Ca^{2+} channels in neonatal heart cells. Accordingly, single Ca^{2+} channel characteristics were investigated in ventricular myocytes isolated from neonatal New Zealand white rabbits (2-5 days) using the cell-attached patch clamp technique. Cell membrane potentials were zeroed by bathing the cells in solution containing 140 mM K^{+} -aspartate. The recording pipette solution contained 110 mM Ba^{2+} . A test depolarization to +10 mV from a holding potential of -80 mV elicited unitary currents of 0.96 ± 0.01 pA (mean \pm SEM, $n=12$) at a temperature of 23°C, similar to single L type Ca^{2+} channel currents measured in other preparations. Ca^{2+} channel open times ranged from 0.6 to 3.8 ms with a mean of 1.9 ± 0.1 (n=12). At least 1 channel opening was observed in 75 percent of 100 ms depolarizations. Averaging 81 depolarizations with channel openings, the mean open time of the channel over the 100 ms clamp period was 3.65 ± 0.27 ms indicating a small open-state probability (P_{open}) of the channel. No superposition of channel openings were measured in these 12 neonatal cells suggesting a low channel density. The results demonstrated that single Ca^{2+} channel activity can be recorded in neonatal ventricular myocytes. We speculate that the lower P_{open} and channel density may contribute to the smaller macroscopic Ca^{2+} current in immature heart cell.

3

Na⁺-Ca²⁺ EXCHANGE CURRENT IN ISOLATED NEONATAL CARDIAC MYOCYTES

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Immature cardiac myocytes are deficient in sarcoplasmic reticulum and are dependent on transsarcolemmal Ca²⁺ influx for tension generation. However, the current density of voltage-gated Ca²⁺ channels is smaller in neonatal than adult rabbit myocytes. Accordingly, we have measured Na⁺-Ca²⁺ exchange current (I_{Na-Ca}) in ventricular myocytes isolated from 1 to 5 day old rabbits using the whole cell voltage clamp technique. Na⁺ and K⁺ channels are blocked with tetrodotoxin, Cs⁺, and tetraethylammonium. Internal Ca²⁺ is buffered with ethylene glycol bis-(β-aminoethyl ether) tetraacetic acid (EGTA). Outward I_{Na-Ca} (outward Na⁺ current/inward Ca²⁺ current) is measured during ramp depolarizations (internal [Na⁺]=20 mM). I_{Na-Ca} is time independent and increases exponentially with membrane potential. I_{Na-Ca} current density at 0 mV increases from 0.64±0.03 to 1.67±0.17 and 2.52±0.16 μA/cm² in 0.1, 1 and 10 mM external Ca²⁺ respectively (mean±SEM, n=4). I_{Na-Ca} is decreased by increasing concentrations of external Na⁺ (1.69±0.14, 1.50±0.10, 0.88±0.11 μA/cm² in 40, 80 and 120 mM Na⁺, respectively, n=5). I_{Na-Ca} is also inhibited by external Ni²⁺ and low internal Ca²⁺. These currents are roughly comparable to peak Ca²⁺ influx via voltage-gated Ca²⁺ channels in neonatal myocytes (4.3±0.4 μA/cm², n=18, in 10 mM Ca²⁺). However, in contrast to Ca²⁺ influx via voltage-gated Ca²⁺ channels, I_{Na-Ca} does not inactivate rapidly. Thus I_{Na-Ca} may provide a significant component of Ca²⁺ influx during contraction in immature myocardium.

4

DEVELOPMENTAL ELECTROPHYSIOLOGIC EFFECTS OF PROPafenONE, 5-HYDROXYPROPafenONE, AND ETHMOZINE ON THE CANINE PURKINJE FIBER

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This study compares the electrophysiologic effects of propafenone (P), 5-hydroxypropafenone (5OP), and ethmozine (E) on the transmembrane action potential (TAP) of Purkinje fibers from adult and neonatal canines. Using microelectrode techniques, either P, 5OP or E were serially superfused for 20 minutes at concentrations of 1 x 10⁻⁷M through 1 x 10⁻⁵M. Maximum action potential amplitude (AMP), maximum diastolic potential (MDP), phase 0 depolarization (V_{max}), and action potential duration at 50% (APD₅₀), and 90% repolarization (APD₉₀) were compared before and after each drug concentration. **Results:** All compounds showed similar concentration dependent depression of V_{max} and amplitude in both age groups. For repolarization effects, however, there were significant developmental differences exhibited by all compounds. P, 5OP and E all significantly shortened APD₉₀ in the adult, while the neonatal APD₉₀ was not statistically shortened and sometimes lengthened. **Conclusion:** P, 5OP, and E all show similar depressant effects on depolarization of adult and neonatal Purkinje fibers. All compounds, however, exhibit similar maturational differences in their effects on the repolarization length of the canine Purkinje TAP.

5

EFFECT OF MITOCHONDRIAL CA⁺⁺ CONTENT ON OXIDATIVE PHOSPHORYLATION IN THE NEWBORN HEART.

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We hypothesized that; in newborn heart mitochondria (M), a measured change in M Ca⁺⁺ does not affect oxidative phosphorylation (O-P); but they depend on extra-M ADP for O-P stimulation. Hearts (n=5) from newborn piglets were removed and perfused with 1 mM EGTA and M were isolated by differential centrifugation. Five other hearts were not perfused and their M were used as controls. Both M (perfused and control) were loaded with fura-2/AM and Matrix Ca⁺⁺ was measured using a 4-channel fluorometer/spectrophotometer. M (without fura) were then incubated with 10 mM of pyruvate, glutamate or α-ketoglutarate as well as ATP and ADP. State 3 & 4 rates of O₂-consumption (nAO/mg/min) were measured by Clark electrode.

	Perfused M	Control M	P
Ca ⁺⁺ (uM)	0.016±0.008	0.1±0.01	<0.0001
S3:Pyruvate	258±26	319±58	NS
S3:Glutamate	199±25	253±39	NS
S3:α-KG	220±36	260±37	NS

Conclusions: (1) M Matrix dehydrogenases for the substrates tested were not affected by lowering Ca⁺⁺ content significantly. (2) O-P in newborn heart M is stimulated mainly by extra-M ADP.

6

REGULATION IN CARDIAC CELL CULTURE OF A GENE ACTIVE IN EMBRYONIC AND HYPERTROPHIED HEART

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Since the alpha smooth muscle actin (ASMA) gene is only active in myocardium in the pre-loop heart and in cardiac hypertrophy in the post-natal heart, the mechanisms of its activation are of great interest. Because gene activation and inactivation are in part the results of nuclear proteins binding at specific DNA sequences, we examined DNA sequences from the promoter (a key regulatory region) of the ASMA gene for function in cultured cardiac cells. We created 15 mutations by progressively shortening a 690 base pair (bp) fragment of the ASMA promoter. The mutations were linked to the protein coding portion of the chloramphenicol acetyltransferase (CAT) gene. The hybrid genes were transfected into cultured embryonic cardiac myocytes (CaM) and embryonic skeletal myoblasts (SkM) and the resulting CAT enzyme activity measured.

In CaM, the ASMA gene is active, and the hybrid genes showed high levels of CAT activity for the 7 deletions between -173bp and -400bp. In contrast, SkM, in which the ASMA gene is inactive, showed low CAT activity for the same deletions. Promoter mutations of 155bp or less were regulated in the same fashion by both cell types. The longest promoter sequences (690, 600, 500bp) showed low CAT activity in CaM.

Conclusions: 1. DNA sequences from -155bp to -173bp contribute to cell type-specific regulation. 2. The first 155bp of the ASMA promoter contains DNA sequences with identical regulatory roles in CaM and SkM. 3. Because the largest promoter fragments tested were of low activity when the endogenous ASMA gene was highly active, there are probably additional DNA regulatory sequences outside of the region examined. We speculate that mechanisms determining cardiac cell differentiation and cardiac cell hypertrophy may be fundamentally similar and that these mechanisms may be utilizing DNA regulatory sequences in the ASMA promoter in common.

SURGICAL EFFECTS IN THE NEURAL CREST-ABLATED MODEL OF HEART DEFECTS.

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In chick embryos, ablation of premigratory neural crest for the third, fourth, and sixth aortic arch arteries frequently results in persistent truncus arteriosus and interrupted aorta. Studies in early cardiogenesis have shown in experimental neural crest-ablated embryos (EXP) decreased ejection fraction (EF) and ventricular dilatation in order to maintain cardiac output (CO). The EXP that survive to cardiac maturity have a higher CO than unoperated-CONTROLS. We hypothesized this is due to a surgically-induced decrease in vasculature resistance (VASC. RESIST.) of the embryonic and vitelline vessels in the EXP. We measured EF and CO by cinephotography, and mean dorsal aorta and diastolic ventricular (approximates mean atrial) pressures by the Servo-Null pressure technique, to calculate VASC. RESIST. We studied 15 unoperated-CONTROLS, 8 SHAM-operated, and 13 EXP chick embryos at the looped cardiac tube stage (stage 18). The SHAMS are identical to the EXP except neural crest is not ablated. Data are expressed as $\bar{X} \pm$ S.E.M., with $p < 0.05 = *$.

	EF (%)	CO (mm ³ /min)	VASC. RESIST. (mmHg x min/mm ³)
CONTROLS	96 \pm 0.9	23.4 \pm 3.7	0.022 \pm 0.004
SHAMS	94 \pm 2.5	32.9 \pm 4.2	0.015 \pm 0.005
EXP	87 \pm 2.7	32.3 \pm 4.4	0.014 \pm 0.006

We conclude that the EXP have a decreased EF compared to SHAMS or CONTROLS. However, there is a trend for the CO to be elevated in SHAMS and EXP. Also, the VASC. RESIST. is decreased in both the SHAMS and EXP indicating this is a result of the sham-effect of surgery rather than of neural crest-ablation. We speculate that re-sealing of the eggshell may cause hypoxemia in the SHAM and EXP. Decreased VASC. RESIST. and increased CO may be compensatory mechanisms to improve oxygen delivery.

HEMODYNAMIC EFFECTS OF EPINEPHRINE & CAFFEINE AND NEURAL CREST ABLATION IN THE STAGE 18 CHICK EMBRYO. *Roger B. Lane and David M. Connuck, FAAP, Dept of Pediatrics, Medical College of Georgia.

Epinephrine (EPI) and caffeine (CAF) induce outflow septation defects similar to those induced by neural crest ablation in chick embryos. We hypothesized that EPI + CAF produce cardiac defects via the same physiological alterations as are seen after neural crest ablation. The purpose of this study was to compare the hemodynamic effects of EPI + CAF with those of neural crest ablation. Ringer's solution (CRL) (n=33) or EPI + CAF (in dosages known to cause outflow septation defects) (n=9) was applied to the chorio-allantoic membrane overlying the heart of stage 14 (day 2 of 21 days incubation) chick embryos. Hemodynamic measurements, including heart rate (HR), cardiac output (CO), shortening fraction (SF), truncal width (TW) and truncal length (TL) were measured at stage 18 (day 3) by microcinephotography. These same measurements were made at stage 18 for 25 neural crest-ablated embryos (EXP) and 23 sham-operated embryos (SHAM). Results are presented as mean \pm SEM, $p < 0.05 = *$ compared to respective controls.

Group	HR (BPM)	CO (mm ³ /min)	SF (%)	TW (mm)	TL (mm)
CRL	174 \pm 3	45.2 \pm 1.9	66.5 \pm 1.5	0.40 \pm .01	0.57 \pm .01
EPI + CAF	187 \pm 2*	47.8 \pm 4.1	76.5 \pm 3.3*	0.36 \pm .01*	0.51 \pm .01*
SHAM	171 \pm 3	55.9 \pm 2.5	47.8 \pm 2.8	0.43 \pm .01	0.48 \pm .02
EXP	168 \pm 4	60.8 \pm 2.5	49.5 \pm 1.7	0.44 \pm .01	0.49 \pm .02

EPI + CAF increased HR and SF and decreased TW and TL. Neural crest ablation had no effect on these properties compared to SHAM. We conclude that the hemodynamic effects of EPI + CAF on the stage 14 to 18 chick embryo are not similar to those of neural crest ablation. We speculate that EPI + CAF may cause outflow septation defects by increasing truncal contractility and not by inhibiting the migration or function of neural crest cells.

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ROMANO-WARD FAMILIAL LONG QT SYNDROME (RWLQTS): MOLECULAR GENETIC EVIDENCE AGAINST LINKAGE TO CHROMOSOME 6p INCLUDING THE HLA REGION. Jeffrey A. Towbin*, R. Michael Giuffre, David Miller, Xue M. Zhu, Edward R.B. McCabe, FAAP, J. Fielding Hejtmancik. Department of Pediatrics (Cardiology), Baylor College of Medicine.

RWLQTS is characterized by QT interval prolongation \pm T wave abnormalities on ECG, stress-induced syncope, sudden death due to ventricular tachycardia, and autosomal dominant inheritance without hearing loss. Previous localization of the gene causing RWLQTS to the HLA region on the short arm of chromosome 6 (6p) by HLA typing has been controversial. Therefore, we used DNA probes within and flanking the HLA region on 6p to clarify linkage in this region in 6 families with RWLQTS. Using Southern blotting and polymerase chain reaction (PCR) dinucleotide repeat polymorphisms, evidence against tight linkage of RWLQTS to the HLA complex was provided by probes pCH6 (lod score = -3.6, $\theta=0$), HLA-B7 (lod = -7.0, $\theta=0$), C4 (lod = -1.2, $\theta=0$), HLA-DR β (lod = 0.13, $\theta=0$), and dinucleotide repeat D6S89. Multipoint analysis excluded linkage in our families with a lod score of less than -2.0, in a region extending from 1cM centromeric of DR β to 5cM telomeric of pCH6. Conclusion: Either RWLQTS lies outside the HLA complex and chromosome 6p, or genetic heterogeneity exists for the LQTS.

GLUTARALDEHYDE CROSSLINKING ENHANCES Ca²⁺ BINDING TO TYPE I COLLAGEN IN VITRO Barbara L. Ciesliga, Lisa D. Barkasi, Catherine L. Webb, MD, FAAP*

Glutaraldehyde preserved bioprosthetic heart valves commonly degenerate due to pathologic calcification. Collagen is the primary structural protein of these bioprostheses. This study was designed to test *in vitro* the hypothesis that collagen crosslinking secondary to glutaraldehyde treatment enhances Ca²⁺ binding. Type I collagen was prepared from immature rat tail tendons (male, CD, Sprague-Dawley, 150-200gm), and crosslinked with 0.6% glutaraldehyde (24hrs, 25°C). Crosslinked and non-crosslinked collagen were dissolved (0.05mg/ml) in a phosphate buffer containing electrolytes including 4meQ/L Ca²⁺ with 0.0025mM/ml ⁴⁵Ca²⁺. The two groups were incubated (37°C) for 21 days. At various time points, ⁴⁵Ca²⁺ binding was assessed by liquid scintillation counting after filtration. For the first five days of incubation, results showed no significant Ca²⁺ uptake in either group. However, by 21 days, the crosslinked collagen bound a significantly greater amount of Ca²⁺ than the non-crosslinked group (7.2 \pm 1.6x10⁻² μ g Ca²⁺/mg collagen vs 1.6 \pm 0.8x10⁻⁴ μ g Ca²⁺/mg collagen; n=5). The amount of Ca²⁺ bound to non-crosslinked collagen after 21 days was not significantly greater than that bound after 1 day (1.6 \pm 0.8x10⁻⁵ μ g Ca²⁺/mg collagen vs 0.0 \pm 2.0 x10⁻⁵ μ g Ca²⁺/mg collagen; n=5). We conclude that glutaraldehyde crosslinking enhances the affinity of collagen for Ca²⁺ binding.

CHARACTERIZATION OF THE RATE-DEPENDENT EFFECTS OF ETHMOZINE ON CONDUCTION IN THE NEWBORN HEART
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Ethmozine (E) is a sodium channel blocking agent with significant antiarrhythmic activity. We studied the effects of E on His-Purkinje (HP) and intraventricular (IVR) conduction utilizing intracardiac stimulation and electrogram recording techniques in 8 newborn canines (8-15 days) following an intravenous dose of E (3 mg/kg bolus; 25-50 mcg/kg/min). All neonates were pretreated with propranolol (1 mg/kg IV) and surgically vagotomized. At rest E increased the HV interval by 15.8% ($p < .03$). During direct His bundle pacing at increasingly shorter cycle lengths (300-60 ms), E resulted in clear rate-dependent HP conduction slowing ($p < .001$) with conduction times exceeding control ($p < .01$) at paced cycle lengths < 220 ms. The time to reach steady state conduction slowing exceeded 40 depolarizations at paced rates ≤ 200 ms. Electrograms recorded from the RV apex became fractionated and increased in duration ($p < .001$) after E. His bundle extrastimulation was performed (S1S₁ = 200 ms, S1S₂ = 500-160 ms) and exponential curve fitting of the data revealed a time constant of recovery from rate-dependent conduction slowing of 131 ms. We conclude: 1) E causes rate-dependent changes in HP and IVR conduction in the newborn. 2) The kinetics (onset and recovery) of conduction delay in the newborn are reported, allowing predictions of E's activity in vivo.

LIPOPROTEIN PROFILES IN HYPERCHOLESTEROLEMIC CHILDREN Richard E. Garcia, M.D., Douglas Moodie, M.D., Cleveland Clinic Foundation, Cleveland, Ohio

Atherosclerosis is a process that begins in childhood. Coronary heart disease is the result of complex interactions among a variety of risk factors of which hypercholesterolemia is but one.

A routine cholesterol screening of 6,500 children after 3 years of age was carried out in a private pediatric practice over a 2-year period in Cleveland, Ohio. Five hundred children were identified to have total cholesterol levels above the 95th percentile of 5.2 mmol/L (200 mg/dL). Lipoprotein profiles were carried out on these children to confirm and delineate their lipid abnormalities.

A definable lipid disorder was present in 85% of this population. Abnormal lipoprotein patterns included 292 children with Type IIA, 99 children with Type IIB, and 25 children with Type IV phenotypes. An abnormally low HDL cholesterol level of less than 0.9 mmol/L (35 mg/dL) was observed in 20 children.

Only 5% of patients were originally diagnosed as having hypercholesterolemia because they had HDL cholesterol levels above the 95th percentile of 1.8 mmol/L (70 mg/dL). Thirty-two percent of the children with total cholesterol levels above 5.2 mmol/L (200 mg/dL) had a family member (sibling, parent, aunt, uncle or grandparent) with a myocardial infarction prior to 55 years of age. Data from the study supports universal cholesterol screening after 3 years of age. Lipoprotein profiles are indicated for those children with levels above 5.2 mmol/L (200 mg/dL) or with a family history of premature heart attack or known hypercholesterolemia.

THE EFFECTS OF ANABOLIC STEROID USE IN THE YOUNG MALE ADULT WEIGHT LIFTER: Thomas Sachleben, Daniel Gwartney, Kris Berg, PhD, John Cheatham, MD, FAAP(C), Barbara Elias, Philip Hofschire, MD, FAAP(C)*. University of Nebraska Medical Center, Omaha, Nebraska

To determine the effects of anabolic steroids on cardiovascular fitness, body composition, cardiovascular function, lipid metabolism and blood chemistry values, we evaluated an age matched group of weight lifters who either used "U" (10 pts) or did not use "NU" (10 pts) anabolic steroids. All subjects had a five year weight training history of at least three times weekly, >one hr/session. Steroid history was of at least three months duration at the time of the study. The U group also had chemistry measurements while off the steroid cycle for four weeks. Results while off cycle indicated serum cholesterol to be equal: U-162mg/dl, NU-162mg/dl, although HDL-C values varied significantly: U-33mg/dl, NU-49mg/dl with resulting chol/HDL ratios of 3.5 and 5.1 respectively. Similar results were evident while taking steroids. Three of the U group had abnormal BUN's and four had abnormal creatinine. Echocardiographic measurements for LV mass, LVDD, LVSD and IVS size did not vary for the two groups. There was no statistical difference in cardio-vascular fitness as measured by VO₂ max. These studies indicate significant differences in HDL-C levels in steroid users even when off cycle. The long term implications of low HDL-C level suggests greater likelihood of coronary artery disease in those who use steroids over a long period of time.

CATHETER RADIOFREQUENCY ABLATION OF ACCESSORY PATHWAYS IN PEDIATRIC PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME

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To eliminate tachycardias associated with accessory pathways (APs) in Wolff-Parkinson-White syndrome (WPW), we pursued catheter ablation of APs in 27 patients (Pts) using radiofrequency current (RF; 30-35 Watts) and deflectable large-tip electrode catheters. Ablation was not performed in 2 pts: one had a right anteroseptal AP adjacent to the His bundle (parents' choice) and the other had neither inducible tachycardia nor retrograde AP conduction. Thus 17 boys and 8 girls (age 2-18 years, mean 12.4 years) underwent ablation, with 8 Pts under age 10 years. Atrioventricular reciprocating tachycardia (AVRT) was present in 17 Pts, atrial fibrillation in 1, both in 2, and the permanent form of junctional reciprocating tachycardia in 4; one Pt had no inducible tachycardia but the AP conducted both antegradely and retrogradely. Three Pts had 2 APs. The distribution of the APs were:

	bidirectional (n=17)	concealed (n=11)
left free wall	9	4
right free wall	4	1
right posteroseptal	2	6
right septal	2	0

After 1-20 RF impulses (median 4), tachycardia was no longer present in 24 of 25 Pts (96%). Fluoroscopy time was 11.6-85 (mean 46.4) mins (n=10). Echocardiograms after ablation revealed no new changes. Peak creatine kinase was 93-4214 (median 290) IU/dl, with MB 0-20% (median 6%) or 0-252.8 (median 12.4) IU/dl. The only complication, pulmonary embolism, occurred in the only Pt in whom the ablation failed. AVRT recurred spontaneously in 2 Pts and both had successful reablation with RF. In summary, RF is highly effective for ablating APs at various locations with few complications and can be considered as the primary treatment modality for WPW in experienced hands.

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LATE VENTRICULAR ARRHYTHMIAS IN PATIENTS FOLLOWING DIRECT CURRENT CATHETER ABLATION OF THE ATRIOVENTRICULAR JUNCTION James Perry FAAP,* Jeffrey Moak FAAP, Richard Friedman FAAP, Debra Kearney, Arthur Garson Jr FAAP. Texas Children's Hospital, Houston, Texas

Early reports of direct current catheter ablation (DCCA) of the atrioventricular (AV) junction for resistant AV tachycardias documented efficacy of DCCA with little morbidity. Eight patients underwent DCCA at our institution 4-9 yrs ago: Three pts had DCCA in the coronary sinus (CS) for permanent junctional reciprocating tachycardia (PJRT), 2 pts had His ablation, 2 had CS and His ablation for PJRT and one had DCCA for congenital junctional ectopic tachycardia. Shocks (total 1-5) ranged from 12.5-400 joules. Five pts had pacemaker implant at the time of DCCA. During follow-up, 3 pts have developed clinical ventricular tachycardia (VT): all 3 had DCCA of the His bundle. One asymptomatic VT pt, who had DCCA of the bundle of His, died suddenly 6 yrs later with ventricular fibrillation. Autopsy revealed two ventricular scars: 1 extending from the AV junction, 1 in the outflow tract. No patient with DCCA limited to the CS developed VT. The junctional tachycardia pt has right bundle branch block and a pacemaker, but no ectopy. **Conclusions:** DCCA of the His bundle can result in late ventricular arrhythmias, possibly a result of extension of the DCCA lesion into the ventricle. These late findings should be considered in evaluating safety and efficacy of radiofrequency ablation.

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COMPUTER GUIDED SURGERY FOR TACHYARRHYTHMIAS: CURRENT RESULTS AND EXPECTATIONS

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Advances in computerized mapping techniques have had a positive impact on surgical results in children with tachyarrhythmias. 1. Success rates for 210 patients from 3 time periods during the evolution of surgery for supraventricular tachycardia due to accessory pathways were:

Pre Computer Era 1977-82 N=41 Success= 80.5
1982-88 86 95.3

Post Computer Era 1988-91 83 100.0

Average age was 11.5 yrs. and operative mortality was 0.48%. Computer enhanced methods successfully diagnosed multiple pathways in 19% of patients. 2. Surgery for atrial ectopic tachycardia was performed in 35 children (mean age 8.6 yr.). Multiple foci were present in 26%. Cryoablative techniques were successful in eliminating tachycardia in 94.3% (33/35) of patients with no mortality. 3. Operative mapping and excision, cryoablation or both eliminated tachycardia in 96.2% (25/26) of infants under 2 yrs. with ventricular tachycardia. Myocardial hamartomas were responsible for tachycardia in 62% (16/25). 4. Surgery eliminated tachycardia in 4/4 patients with A-V node re-entry tachycardia and 15/15 patients with the permanent form of junctional reciprocating tachycardia. Definitive surgery aided by new computerized mapping techniques is currently a safe and predictable therapeutic option in the treatment of tachyarrhythmias.

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SURGICAL THERAPY OF ATRIAL FLUTTER AFTER MUSTARD'S OPERATION: AN EXPERIMENTAL MODEL James Perry FAAP*, Kathy Sprague, Hiroyuki Noda, Ryosuke Matsuwaka, Arthur Garson Jr FAAP. Texas Children's Hospital and Texas Heart Institute, Houston, Texas

Early survival and hemodynamic results of Mustard's operation (MO) are excellent, but late atrial flutter (AFL) is correlated with sudden death. An animal model of MO was developed in 15 beagles to investigate potential surgical therapy for AFL. An atrial baffle is placed as in MO, but the material is excised, leaving an intact suture line. The atrial septal defect is closed. There were 4 immediate post-op deaths and 1 late "unexpected" death. Of 10 survivors, 8 had inducible AFL 3-4 months post-op. AFL was induced by atrial extrastimuli or rapid pacing, terminated by overdrive pacing and did not show "warm-up". The AFL cycle length ranged from 160-205 msec. Epicardial mapping was performed with a 40-46 pair electrode plate. An area of slow conduction was present near the right lateral suture line in 7/8. Fractionated electrograms were found around the atriotomy. Epicardial activation during AFL was "early" (compared to flutter wave) in the posteroinferior atrial groove in 4 dogs with apparent circuit around the tricuspid annulus. Epicardial cryoablation of this region in 3 dogs resulted in termination of AFL in 2. **Conclusion:** Suture lines and slow conduction provide the substrate for AFL. Epicardial mapping of AFL is feasible and surgical therapy for AFL in selected post-op MO patients may be beneficial.

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EPICARDIAL PACING IN THE YOUNG: EVALUATION OF STEROID-ELUTION AND NEW ELECTRODE SURFACE

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Steroid (S) elution at the pacing electrode-tissue interface may attenuate fibrosis (F) and inflammation (I) resulting in low pacing threshold (Th). Since a microporous (MP) electrode (E) surface itself also reduces F and I, Th-lowering effect and need for S-elution with the new MP design are unknown for epicardial (Epi) E. This study reports the first clinical comparison of two new low Th Epi E in 13 children (mean age 10.4y): Medtronic lead models 10295A (surface area 14.4mm²) (n=5) and 4951-P (10mm²) (n=8). Both surfaces are MP plated platinum with <1mg dexamethasone in the model 10295A only. Both leads were used for atrial (A) and ventricular (V) pacing. At implant mean values showed comparable (p=NS) A and V sensing (mV), Th energy (uJ) and impedance (Ω):

	A	V	Energy	Impedance
4951-P	2.6	15	0.8	416
10295A	1.7	10	0.9	476

Due to pulse generator variability, chronic Th analysis compared mean energy (uJ) at 500Ω for both E at low output (2.5 or 2.7 volts):

	1wk	2wk	3wk	4wk	8wk	12wk	24wk
4951-P	1.3	2.1	3.0	2.1	2.6	3.2	2.3
10295A	2.0	1.7	1.2	1.0	1.2	1.0	0.6
p Value	NS	NS	NS	NS	.05	.05	.01

CONCLUSION: this initial study shows that the addition of S augments low Th capabilities of MP platinum Epi E. New S-Epi E will permit use of small, low energy generators in children.

THERAPEUTIC AND DIAGNOSTIC USE OF ADENOSINE DURING EVALUATION OF CHILDREN WITH TACHYCARDIA

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Adenosine is a naturally occurring nucleoside, the safety and utility of which has not been thoroughly evaluated in children with tachycardia. We reviewed our experience with adenosine to assess its efficacy in terminating tachycardia and establishing arrhythmia mechanism. We gave 131 doses of adenosine to 40 children (age 3 days - 20 yrs, median 12 yrs) during 57 separate electrophysiologic evaluations. 38/40 had documented narrow QRS tachycardia (28 orthodromic reciprocating tachycardia), and 2/40 had wide QRS.

Adenosine was given during tachycardia in 29/57 studies, resulting in termination in 25 of the 29 (86%). Further diagnostic information was sought in 36/57 studies and was obtained in 34 of the 36 (94%). Given by rapid intravenous bolus, doses ranged from 50 to 350 mcg/kg, mean 129 ± 52 . Peripheral administration was effective in 19/25 doses, central in 21/24 doses. Higher peripheral than central doses were required for tachycardia termination (163 ± 52 mcg/kg vs 113 ± 38 mcg/kg, $p < .01$). Sustained tachycardia spontaneously recurred in 4/30 patients within 1 minute of adenosine administration. Potentially serious side effects occurred in 4 patients, including 1 each of transient apnea, >1 minute asystole requiring resuscitation, accelerated ventricular tachycardia, and atrial fibrillation. Mean adenosine dose for these 4 episodes was 138 mcg/kg.

Our data demonstrate that adenosine may be useful therapeutically and diagnostically in infants and children with tachycardia. Larger doses may be required for efficacy in peripheral IV administration. Serious side effects, though not common, should be anticipated.

ELECTROCARDIOGRAPHIC AND ELECTROPHYSIOLOGIC FEATURES OF PATIENTS WITH ATRIAL ISOMERISM

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Pathologic examinations of human hearts having atrial isomerism have revealed double atrioventricular nodes and His bundles with a sling of conduction tissue linking them. We describe ECG(4) and electrophysiologic(3) properties of 4 pts with right-(RSI) or left-sided isomerism(LSI) and complex heart disease. Three (2 RSI, 1 LSI) had 2 atrial pacemakers, with inferior P axes in both with RSI and superior in 1 with LSI. Every change in P axis had a specific PR interval and QRS morphology. P axis change preceded PR interval and QRS change within 2 beats. Ventriculoatrial conduction(VAC) was absent in 1 pt with RSI; present, concentric, and decremental in the other; and decremental in 1 with LSI. Atrioventricular conduction (AVC) was always decremental. An accessory electrogram was observed in 1 each with RSI and LSI. It followed the QRS, had decremental anterograde properties, and blocked prior to atrioventricular block. Arrhythmias observed included: paroxysmal supraventricular tachycardia (SVT) in 1 pt each with RSI and LSI; ectopic atrial tachycardia in 1 pt with RSI; and automatic junctional tachycardia in 1 with LSI. We conclude that in pts with atrial isomerism: 1) 2 superior pacemakers exist in RSI; 2) AVC and VAC are decremental; 3) no specific SVT type predominates; and 4) dual junctional conduction systems may exist and are functional. We have described an electrogram which represents a connecting sling between the 2 conduction systems.

EARLY RESULTS AFTER PEDIATRIC CARDIAC TRANSPLANTATION. Charles E. Canter, MD*, FAAP, R. Morton Bolman, MD, Thomas L. Spray, MD, Pediatrics, Washington Univ., St. Louis, Mo.

Use of orthotopic cardiac transplantation (TX) in children has prompted questions about differences in results between infants and older children. We compared the early results of consecutive TX in 10 infants (median age at TX= 30 days; range, 10 days-11 months; median follow-up=9 months; range, 3-18 months) with 8 older children (median age of TX=12 years; range 3-18 years; median follow-up=46 months; range, 27-78 months). All received triple immunosuppressive therapy (prednisone, azathioprine, cyclosporine). Rejection was monitored by endomyocardial biopsy in both groups. 9/10 (90%) infants and 7/8 (87%) children are alive. Both deaths were secondary to pulmonary vascular disease. There were 7 rejection episodes (none symptomatic, all within 6 months of TX) in the older group and 4 episodes in the infant group (1 symptomatic, all within 3 months of TX). 1 episode of infection in each group (pneumonia) required hospitalization. Complications included renal failure with dialysis (1 infant, 1 adolescent); phrenic palsy (1 infant), intracranial bleed with seizures (1 infant), and ventricular fibrillation (1 infant). Posttransplant hospital stay was significantly ($p < 0.05$) longer and costlier in the infant ($m=27.4$ days; range=10-80 days) than the older group ($m=19.4$ days; range=11-48 days). Thus, TX with triple drug immunosuppression has a similar low early mortality, low incidence of rejection, and low number of significant infections in infants and older children and adolescents.

CYCLOSPORINE VS FK 506 IMMUNE SUPPRESSION IN PEDIATRIC HEART TRANSPLANTATION

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Since 1989 with the introduction of the clinical use of FK506 immune suppression, 15 children have received FK506 as primary immune suppression after orthotopic heart transplantation (OHT). We compared their course over the first year after (OHT) with 15 recipients receiving cyclosporine (CYLA) based immune suppression between 1985-1989. The CYLA group also received induction therapy with antithymocyte globulin (ATG) and maintenance therapy with azathioprine 1-2 mg/kg/day and prednisone (0.1-0.3 mg/kg/day).

	CYLA	FK506
Age	5-17yr (m-12)	1-15yr (m-4)
Indication: CAR/CHD	9/6	8/7
Survival	14/15	14/15
Actuarial free/rej.	10%	50%
Linear rejection episodes (100 pt/days)	.62	.44
Hypertension (Rx)	11/15	1/15
LDL cholesterol	144 mg% \bar{m}	92 mg% \bar{m}
Prednisone (maint)	10/14	2/14

In summary, FK506 is comparable immune suppression to CYLA for pediatric OHT. Prednisone is not required for maintenance immune suppression and incidence of hypertension and hyperlipidemia is low.

OCGULT RESTRICTIVE HEMODYNAMICS AFTER PEDIATRIC HEART TRANSPLANTATION

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Right heart hemodynamics are routinely measured in children undergoing surveillance endomyocardial biopsy after transplant (HT). After baseline hemodynamics were obtained (B), we performed fluid challenges in 20 patients (Pts) age 1 to 16 yrs from 6 months to 6 years after HT. Normal saline infusion 10 cc/kg was administered intravenously as a bolus and hemodynamics and thermodilution cardiac outputs were remeasured. Response to volume expansion (VE) was compared to published controls (Ctrl).

		Mean Pressures ±S.D. (mmHg)		
		RA	RVED	PAW
1. Pts - B		4.2±2.6	4.5±2.4	8.5±2.3
	VE	6.6±3.7	7.9±3.7	15.0±3.5
2. Ctrl - B		2.7±1.2	3.3±1.2	6.3±2.1
	VE	3.6±1.0	5.2±1.2	8.2±2.7

When compared to controls, 11 of 20 had an abnormal hemodynamic response to fluid challenge, but no significant change in cardiac index. Baseline hemodynamics and VE response did not predict biopsy evidence of rejection. Immunosuppression was triple therapy in 16 and FK506 in 4 and no difference was found between these groups. The abnormal increase in CVP, wedge and ventricular diastolic pressures after VE suggests unmasking of restrictive physiology after HT, and may be common. The etiology is unknown but does not appear to be related to chronic rejection, time after HT, or type of immunosuppression.

INTERMEDIATE AND LONG TERM (5 TO 15 YEAR)

SURVIVAL AFTER THE MODIFIED FONTAN OPERATION

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Early results of the modified Fontan operation (MFO) are well documented. In order to determine relatively long term survival and its predictors, we studied 352 pts who had MFO between 1973 and 1985. Follow-up was complete and current in 96%. The pts had 3 groups of lesions: tricuspid atresia (TA, n=125), double inlet left ventricle (DILV, n=114) and complex single ventricle (n=113). The overall 30 day, 1-, 5- and 10-yr survival was 84, 77, 70 and 60%, respectively. Pts with TA had the best outcome (p<0.001), with 5- and 10-yr survival of 80/70%. Those with DILV and complex forms had 5- and 10-yr survivals of 73/57%, and 56/52%, respectively. We studied 15 potential predictors of outcome. Only gender, age ≥16 yrs at operation and abnormal pulmonary artery (PA) architecture did not affect outcome in a univariate fashion. Multivariate analysis showed that early calendar yr of operation, mean PA pressure >15 mm Hg, ventricular anatomy other than TA, AV valve dysfunction, age <4 yrs, heterotaxia, and preoperative NYHA class 2, 3, or 4, adversely affect outcome. Combining this information with what is already known about the predictors of early survival should allow more insightful selection of pts for MFO. This, in turn, may ultimately improve long term outcome for these pts.

BIDIRECTIONAL CAVOPULMONARY SHUNTS (BCS)

IMPROVE RISK FACTORS FOR FONTAN

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BCS are now widely performed in patients (pts) with single ventricle, either as a palliative procedure, or with the hope that early BCS will improve Fontan candidacy by diminishing ventricular volume load. The purpose of this study was to evaluate the effect of BCS on Fontan risk factors.

Clinical status, echocardiographic, and catheterization data were reviewed on all pts who underwent BCS between 11/89 and 2/91. Pre and post BCS Fontan risk factors were graded, risk factors were: pulmonary artery (PA) stenosis; pulmonary vascular resistance (PVR)>2 Woods units (WU); PA pressure>18mmHg; significant atrioventricular valve regurgitation; ventricular end-diastolic pressure>12mmHg; and poor ventricular function (lowest possible risk=0, highest=8). Results are expressed as median±standard deviation, differences were evaluated by Wilcoxon matched pairs test.

Results: BCS were performed in 14 pts aged 5m to 15 yrs (6<12M). 4 pts had bilateral BCS, and 2 concurrent PA reconstruction. One pt with PVR of 4.2 WU died on the second postoperative day and 1 required prolonged post-operative ventilation for pneumonia. The 13 survivors had a mean hospital stay of 11±2 days, all are asymptomatic 2-16 months post-op (mean 9±5m). 9 pts have undergone post-operative catheterization. Ventricular volume load decreased from 10.2±4.7 l/min/M2 to 4.2±0.9 l/min/M2 (p<0.05); systemic oxygen saturation increased in 5 and was unchanged in 3 (mean 82±3% post-op). After BCS, 9 therapeutic catheter procedures were performed in 7 patients: 5 PA dilations; 2 dilations of restrictive atrial communications; 1 dilation of an obstructed pulmonary venous anastomosis; and 1 embolization. Risk scores improved in all patients from 2.3±.9 pre to 0.8±.7 post BCS(p<0.05).

Conclusions: BCS performed in high risk Fontan candidates at a young age have a low morbidity, decrease ventricular volume load, and maintain systemic saturation. These beneficial hemodynamic effects combined with surgical and catheter treatment of PA stenoses decrease risk factors for Fontan. It remains to be seen whether this will result in improved long-term function and survival for this high risk group.

IMPROVED SURVIVAL IN HETEROTAXY PATIENTS UNDERGOING MODIFIED FONTAN PROCEDURE

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Mortality remains high for pediatric patients with heterotaxy syndrome who undergo the modified Fontan procedure. We undertook a retrospective analysis of 111 pediatric patients who underwent the Fontan procedure between 1987-1990. Sixteen heterotaxy patients (10 with asplenia and 6 with polysplenia) were identified with an overall mortality rate (early + late deaths) of 18.8% versus 11.6% for the non-heterotaxy patients (p>0.05); a lower rate than previously reported. The effect of early adequate control of pulmonary blood flow by aorto-pulmonary shunt or banding (age ≤ 6 months with a resultant MPAP ≤ 15 mm Hg.) as well as anatomic risk factors are summarized below:

FACTOR	DEATHS / TOTAL	p-value
Early + adequate palliation (achieved : not achieved)	0/13 : 3/3	p < 0.05
AV valve regurgitation (absent : present)	0/11 : 3/5	p < 0.05
Heterotaxy anatomy (polysplenia : asplenia)	0/6 : 3/10	p > 0.05
Ventricular morphology (Single left : single right)	1/7 : 2/9	p > 0.05

We conclude that early and adequate control of pulmonary blood flow results in a significant reduction in the mortality rates seen in heterotaxy patients undergoing the modified Fontan procedure. Also, greater than mild AV valve regurgitation pre-operatively places these patients at a significantly higher risk for a poor outcome. Risk factors such as asplenia and single right ventricle may also have a negative effect on the outcome of heterotaxy patients undergoing the modified Fontan procedure.

PROTEIN-LOSING ENTEROPATHY OF LONG-TERM SURVIVORS OF THE FONTAN OPERATION. Robert H. Feldt, FAAP*, David J. Driscoll, FAAP, Co-burn J. Porter, FAAP, Jean Perrault, Francisco J. Puga, Gordon L. Danielson, Section of Pediatric Cardiology, Mayo Clinic, Rochester, MN

Protein-losing enteropathy (PLE) is an important complication of the Fontan operation. This study assessed the incidence and clinical course of PLE of survivors of the Fontan operated from 1973 to January 1987. Of 340 survivors, data is available on 300 (88%). Twenty-two pts have PLE. Another 9 pts have findings compatible with PLE. Including all 31 pts the incidence of PLE is 10.3% (31 of 300).

All 22 pts with PLE have hypoproteinemia (range 5.9 to 3.0, mean 4.6). Lymphocytopenia was present in 12 of 15 (80%). Alpha-1-antitrypsin clearances varied from 14 ml to 1300 ml. Hemodynamic findings in PLE pts were not different than in other postop Fontan pts.

The clinical course is variable. Six pts require periodic albumin infusions and have had hospitalizations for PLE. Three pts have shown improvement. One pt had transient PLE. The other 12 pts are stable. Length of time with diagnosis of PLE is variable (1 to 12 yrs) as is interval between operation and diagnosis (6 months to 11 years).

Our data suggest that at least 10% of Fontan pts will develop PLE and there is a wide spectrum of severity. All Fontan pts need monitoring for this complication.

FACTORS INFLUENCING LENGTH OF HOSPITAL STAY AFTER SURGERY FOR CONGENITAL HEART DISEASE. David A. Danford, FAAP*, William H. Fleming*, Anthony L. Mowton*, Lynne B. Sarafian*, Thomas G. Tape, University of Nebraska Medical Center, Omaha, NE

A subset of patients treated surgically for congenital heart disease (CHD) accounts for major resource utilization due to long postoperative length of stay (LOS). To identify which factors predict LOS, we assembled a derivation cohort of 480 consecutive patients (age 0-30 years) surviving operation for CHD. We abstracted 19 factors hypothesized to predict LOS and developed a rule to predict LOS > 7 days and LOS > 14 days using stepwise logistic regression. We validated the rule on a second set of 186 consecutive patients.

Median LOS = 6 days (25th-75th tile: 4-9). The independent predictors of LOS were age ($p < 0.0001$), use of cardiopulmonary bypass ($p < 0.0001$), complex anatomy ($p = 0.0005$), simplest anatomy ($p = 0.0001$), pulmonary hypertension ($p = 0.0018$), major defects of noncardiac systems ($p = 0.0048$), and preoperative condition in extremis ($p < 0.001$). The model accurately predicted LOS in the validation cohort with receiver operating characteristic areas of 0.823 and 0.776 for LOS > 14 days and LOS > 7 days respectively. Calibration in the validation cohort is excellent.

Probability of long LOS can be estimated accurately from clinical features known preoperatively. Preoperative identification of high risk patients may allow better planning to reduce morbidity and permit better utilization of hospital resources.

CRITICAL AORTIC STENOSIS: COMPARISON OF BALLOON VALVOTOMY THROUGH THE RIGHT CAROTID ARTERY VS SURGICAL VALVOTOMY

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The results of treating critical aortic stenosis (AS) by balloon valvotomy (BV) through a right carotid arteriotomy are compared to surgical valvotomy (SV) in 21 consecutive neonates (median age 4 days, range 1-29) seen between 1/1/83 and 12/31/90. The first 13 underwent SV and the next 8 BV. The following parameters were compared:

	SV	BV	p
Deaths	8 (62%)	1 (13%)	<.05
Age (days)	6.2±7.8	9.8±10.3	NS
Weight (kg)	3.2±.56	3.4±.34	NS
Aortic Valve (mm)	6.2±1.5	7.3±1.0	NS
Mitral valve (mm)	9.2±1.1	9.1±1.1	NS
LVED dimension (mm)	14.4±1.9	16.8±4.6	NS
LV volume index (ml/m ²)	17.5±5.0	24.0±13.4	NS
LVED pressure (mmHg)	17.3±6.3	18.8±9.3	NS
Index (l/min/m ²)	2.6±.59	2.6±.75	NS
Gradient (mmHg)	73.5±18.1	68.1±18.1	NS
Follow up (FU) (years)	5.6±1.3	1.4±.9	<.01
FU gradient (mmHg)	52.6±22	40.4±11.5	NS

Two patients in each group have required late intervention for residual stenosis 8 months to 2 years after the initial valvotomy. Only 1 patient in each group has moderate AI, the others have only mild or trivial AI. All survivors of BV have a patent carotid artery and none have neurologic sequelae. In conclusion, BV through a carotid arteriotomy is safe and has a lower mortality than SV in the treatment of critical aortic stenosis.

TRANSCATHETER CLOSURE OF VSD IN HIGH RISK PEDIATRIC PATIENTS: Larry A. Latson, M.D., F.A.A.P.*; John P. Cheatham, M.D., F.A.A.P.*; David A. Danford, M.D., F.A.A.P.*; Carl H. Gumbiner, M.D., F.A.A.P.*; John D. Kugler, M.D., F.A.A.P.*; Philip J. Hofschire M.D., F.A.A.P. University of Nebraska Medical Center and Childrens Memorial Hospital, Department of Pediatrics.

Between 8/90 and 2/91, we placed Bard Clamshell Septal Umbrellas® in 10 VSD's in 6 patients (pts) with complex cardiac malformations and significant risk factors for cath and surgery, including small left ventricle (LV) (2), poor LV function (2), pulmonary hypertension (2), and saturation < 75% (2). Pts were 17-78 (mean 42) mos old and weighed 7.1-16.5 (mean 11.9) kg. All catheters were performed under general anesthesia and transesophageal echocardiography aided in identification of the target VSD and confirmation of proper placement of the device in 9/10 catheters. Devices were delivered through an 11 French long sheath which had been positioned through the VSD over a trans-VSD guide wire, with both ends of the guide wire controlled outside of the body.

Catheters were in place for 1.6-5.2 (mean 3.25) hrs. One pt with poor LV function developed seizures progressing to a flat EEG two days after severe instability during the cath. The only other complications included need for transfusion after two procedures, and new ventricular arrhythmias which cleared without treatment within one month after two procedures. Three pts underwent subsequent attempted surgical repair of additional complex lesions 1-3 mos after placement of 1-3 devices. There was nearly complete endothelialization of the devices with closure of the targeted defects. One pt had resolution of pulmonary hypertension and marked improvement in the gradient across a stenotic mitral valve after elimination of the VSD shunt, and one pt is awaiting further intracardiac surgery if growth of the LV can be demonstrated.

Transcatheter closure of VSDs is technically demanding and requires large catheters, but can be performed with reasonable morbidity and mortality in relatively small, high-risk pts.

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SYSTEMIC TO PULMONARY COLLATERAL CIRCULATION IN INFANTS WITH BRONCHOPULMONARY DYSPLASIA (BPD). Henry M. Sondheimer FAAP*, Warren H. Toews FAAP, Reginald L. Washington FAAP, and Steven H. Abman. University of Colorado, Denver.

To study the incidence and potential contribution of systemic to pulmonary collateral arteries in severe BPD we reviewed the clinical course of 17 consecutive infants with BPD who underwent cardiac catheterization during a three year period. Mean age at study was 8 months (range 3-24). Patients were evaluated to rule out anatomic heart disease and evaluate the severity of pulmonary hypertension (PHT). Prominent systemic to pulmonary collaterals were seen by angiography in all but one infant. The most common sites were from the descending aorta (76%), internal mammary arteries (29%), and intercostal arteries (24%). Although most infants had small collaterals, a large artery ($>3\text{mm}$) was found in 3 cases (18%). Each patient with a large collateral had mild PHT (mean PAP 28-43 torr) and responded to coil embolization with clinical improvement in PHT, and O_2 , ventilator, and diuretic use. Two infants with large collaterals did not have retrograde flow by continuous wave Doppler. We conclude that systemic to pulmonary collaterals are frequent in BPD and although seen with angiography they may not be appreciated with non-invasive techniques. These can occur with mild PHT. As embolization of large arteries led to clinical improvement in three cases, we speculate that major systemic to pulmonary collateral arteries may contribute to persistent symptoms in severe BPD.

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FORAMEN OVALE SIZE IN THE HUMAN FETAL HEART: AN INDICATOR OF TRANS-ATRIAL FLOW PHYSIOLOGY. *Lloyd R. Feit, Joshua A. Copel, Charles S. Kleinman, FAAP. Department of Pediatrics, Yale University School of Medicine, New Haven, CT.

The distribution of blood flow between the right and left ventricles may be important in the morphogenesis of the fetal heart and circulatory system. The size of the foramen ovale relative to the atrial septum may reflect in utero flow patterns within the cardiac chambers. To more clearly define the impact of altered trans-foraminal flow in utero, we used fetal echocardiography to measure the sizes of the foramen ovale (FO), and atrial septum (AS) in 84 human fetuses from 18-38 weeks gestation. Forty six had normal cardiac anatomy, 23 had left heart obstructive lesions (LHO), 15 had right heart obstructive lesions (RHO). Pulsed and color flow Doppler studies were incorporated when available. We found that normal fetuses had a FO/AS ratio of 0.33 ± 0.04 (mean \pm SD). All had bidirectional, but predominantly right to left, flow through the foramen ovale. Fetuses with LHO had a FO/AS ratio smaller than normal (0.27 ± 0.05 ; $p < 0.001$). Five of seven demonstrated reversal of the normal flow pattern, exhibiting unidirectional left to right trans-foraminal flow. Those with RHO had a larger than normal FO/AS ratio, (0.47 ± 0.04 ; $p < 0.001$) and had almost exclusive right to left trans-foraminal flow. We conclude that FO/AS ratio, and Doppler interrogation of trans-atrial flow are helpful adjuncts in determining the presence of congenital heart disease in utero. In addition, early detection of abnormal FO/AS ratio may predict whether left or right ventricular development will be impaired through gestation, even before disparity of ventricular size is apparent.

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THE TIMING OF DUCTAL CLOSURE IN VERY LOW BIRTH WEIGHT (VLBW) PREMATURE INFANTS WITHOUT RESPIRATORY DISTRESS SYNDROME (RDS)

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VLBW infants, particularly those with RDS, are well recognized to be at risk for persistent patency of the ductus arteriosus. While we have previously demonstrated that functional closure of the ductus occurs by the 4th day of life in larger premature and fullterm infants without RDS, no information exists for the smallest VLBW infants. Accordingly, to assess the independent risk of lesser gestational age on ductal function, 24 infants 26-30 weeks gestation without RDS (mean Birth Wt=1274 \pm 337 gm) were sequentially studied using color flow Doppler techniques. Infants were evaluated initially in the first 16 hours of life, and then once daily until no ductal flow was detected. Five of the infants (21%) had evidence for ductal closure on the 1st study (10.5 ± 4.9 hrs). Ductal closure was noted on subsequent days in 18 (75%) infants at a mean age of 32.7 ± 6.7 hrs, 21 (87%) infants at a mean age of 56.0 ± 7.3 hrs, and all 24 (100%) infants by a mean age of 78.7 ± 4.8 hrs. No infants received indomethacin. While low gestational age predisposes to RDS which is associated with persistent ductal patency, we conclude from these data that gestational factors alone are not associated with altered ductal function. In the absence of RDS, the timing of physiologic ductal closure occurs normally in even the smallest VLBW infants.

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BIPLANE PEDIATRIC TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN INFANTS AND CHILDREN: ASSESSMENT OF CONGENITAL HEART DISEASE

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The use of transesophageal echocardiography (TEE) in the assessment of congenital heart disease (CHD) has been described including use of pediatric size single plane TEE probes. Heretofore, biplane imaging has not been feasible in small infants because of limitations of TEE probe size. Using a 6.8mm 42-element longitudinal TEE probe in conjunction with a 26-element 6.8mm transverse TEE probe in 30 infants and a prototype biplane 6.8mm pediatric size TEE probe in an additional 23 infants and children ranging from one day to twelve years (mean 35 months) weighing 2.1-40kg (mean=11kg) TEE studies were performed in the operating room pre and post open heart surgery, cardiac intensive care unit postoperatively, cardiac catheterization laboratory, and neonatal intensive care unit. Structural CHD evaluated included VSD, AV septal defects, TOF, TGV, truncus arteriosus, pulmonary atresia, TAPVR, etc. 2 BAS procedures in the neonatal ICU were performed under TEE guidance. Additional information was provided in 75% of the cases. Specifically, RVOT anatomy and AV valve function were better visualized. Biplane TEE imaging with pediatric size probes greatly enhances the evaluation of CHD and its repair in infants and small children.

ECHO/DOPPLER PROFILE DURING MAXIMAL TREADMILL EXERCISE IN CHILDREN WITH VALVULAR AORTIC STENOSIS/INSUFFICIENCY. Stephen E Cyran FAAP, Marek Grzeszczak, Howard S Weber FAAP, Marie M Gleason FAAP Barry G Baylen FAAP, MS Hershey Med. Ctr., Dept. Peds., Hershey, PA.

The Doppler profile during graded treadmill exercise (EX) in normal (N) children and those with aortic valve (AV) stenosis (S) or insufficiency (I) has not been reported. We evaluated 26 children with AV disease (age 10.6 ± 4.2 y, BSA 1.3 ± 0.1) and 27 matched controls (age 10.8 ± 0.6 y, BSA 1.2 ± 0.1) via a Bruce protocol to exhaustion and similar max. predict heart rates ($90 \pm 1\%$; $92 \pm 1\%$). The aortic peak systolic velocity (VEL) and gradient (GRAD) were determined at each EX stage (ST) by CW Doppler exam from the suprasternal notch. Five VEL envelopes were analyzed at each pt/stage. Pts with AV disease were analyzed according to their dominant lesion: Bicuspid AV: (BA) (rest VEL < 2.5 m/sec), AV S: obstructive (AS), AV I (AI), AS/AI VEL (m/sec) results in table (mean \pm SE) (ANOVA, $P < 0.001$, (*) vs N, (+) vs preceding ST).

	REST	ST 1	ST 2	ST 3	PEAK
N	1.2 ± 0.0	1.8 ± 0.1	1.8 ± 0.0	2.0 ± 0.0	2.1 ± 0.0
BA	2.0 ± 0.2	2.5 ± 0.2 *	2.7 ± 0.2 *	2.8 ± 0.2 *	3.0 ± 0.2 *
AS	3.6 ± 0.2	4.6 ± 0.3 *	5.0 ± 0.4 *	5.1 ± 0.4 *	5.3 ± 0.3 *
SI	3.3 ± 0.2	4.0 ± 0.2 *	4.2 ± 0.2 *	4.3 ± 0.2 *	4.8 ± 0.2 *
AI	2.3 ± 0.1	2.8 ± 0.0 *	3.0 ± 0.1 *	3.1 ± 0.1 *	3.2 ± 0.1 *

The greatest relative increase in VEL for all groups was from rest to ST1 (AS: 56%, BA: 48%, N: 60%, AI: 65% AS/I: 69%). The EX GRAD response best fit a 2nd order relation ($R = 0.6$ (AS), 0.7 (BA), 0.7 (N), 0.8 (AI), 0.5 (AS/I); $p < 0.001$). This suggests that children have their predominant EX increase in aortic VEL/GRAD during early exertion. This has implications regarding their EX prescription.

STRESS ECHO/DOPPLER EXPLAINS EXERCISE INDUCED "ESSENTIAL HYPERTENSION" IN CHILDREN FOLLOWING REPAIR OF COARCTATION OF THE AORTA. *Stephen E Cyran FAAP, Marek Grzeszczak, Howard S Weber, Marie M Gleason FAAP, Barry G Baylen FAAP. Dept Peds, MS Hershey MedCtr, Hershey, PA.

We performed stress echocardiography (echo) in 14 children (11.6 ± 1.0 yrs) who had undergone surgical repair of coarctation of the aorta and were free of aortic valve stenosis and descending aortic (DA) obstruction (OB) as determined by 2D-Doppler echo. They were compared to 27 matched controls (N) (10.9 ± 0.6 yrs). All underwent maximal treadmill exercise (EX) (Bruce protocol) to exhaustion and similar % max predicted HR (94 ± 2 vs 92 ± 2 , P vs N) and EX duration (13.4 ± 0.6 vs 13.4 ± 0.6 mins). DA peak systolic velocity (PSV) was interrogated via CW Doppler at rest (R), sub-max EX (ST1, ST2, ST3), and peak EX. Five PSV were evaluated for each Pt/stage. PSV results in table (m/sec) (mean \pm SE) ($p < 0.001$) (*) vs N, (+) vs preceding EX stage).

	R	ST1	ST2	ST3	PEAK
P	2.4 ± 0.1 *	3.0 ± 0.2 *	3.3 ± 0.2 *	3.5 ± 0.2 *	3.7 ± 0.2 *
N	1.4 ± 0.1	1.9 ± 0.1	2.1 ± 0.1	2.2 ± 0.1	2.2 ± 0.1

The DA gradient at peak EX was 55 ± 3 vs 19 ± 1 mmHg, P vs N, $p < 0.001$. No pts had a diastolic velocity (DV) or hypertension at rest. 5/14 pts developed DV during exercise vs 0/27 controls ($p < 0.01$). 7/14 pts developed EX induced systolic hypertension. Systolic blood pressure (SBP) at peak EX was explained by apparent DA OB (PSV) and pt's age: $SBP = 7.7(\text{age}) + 21.8(\text{PSV}) - 7.3$, $p < 0.0001$, $R^2 = 0.90$. EX induced hypertension in pts without DA OB at rest following repair of coarctation is due to relative OB during exercise. This may be due to a "noncompliant" region at the site of repair.

CARDIAC TOXICITY BEFORE AND AFTER BONE MARROW TRANSPLANTATION. Ranae L. Larsen,* Gerald Barber, FAAP, Charles T. Heise, and Charles S. August, FAAP. The Children's Hospital of Philadelphia, Philadelphia, PA.

Cardiac toxicity may occur secondary to the anthracyclines (A) and radiation (XRT) used in preparation for bone marrow transplantation (BMT); its prevalence and degree are unknown. We hypothesized exercise testing, with measurements of O_2 consumption (VO_2), cardiac index (CI), and ventilatory anaerobic threshold (VAT), would detect abnormalities not found at rest.

Methods: Pts before ($n = 20$) and at least 1 yr after BMT ($n = 31$) performed cycle ergometry. Mean age at testing was 14.5 yrs. Mean A dose was 135 mg/m^2 in the group before and 131 mg/m^2 in the group after BMT. Pts received 300-1200 cGy of total body XRT before BMT. CI was determined via the acetylene-helium rebreathing technique. Results were compared to 77 laboratory normals. Left ventricular shortening fraction (SF) at rest was assessed via echocardiography.

Results: VO_2 and CI at rest were normal both before and after BMT. SF was 0.33 ± 0.04 before and 0.33 ± 0.03 after BMT. Exercise testing detected significant abnormalities:

Parameters	Before BMT u \pm SD	After BMT u \pm SD	Normals u \pm SD
Max VO_2 (ml/min/kg)	21 ± 4 *	24 ± 6 *	35 ± 7
Peak CI (l/min/m ²)	7.4 ± 1.6 *	7.0 ± 1.7 *	9.1 ± 1.4
Peak SVI* (ml/m ²)	44 ± 9 *	41 ± 10 *	51 ± 7
VAT (ml/min/kg)	15 ± 3 *	16 ± 4 *	21 ± 6

*SVI = stroke volume index

Conclusions: 1) Abnormalities of exercise cardiac performance are detected in most pts before and after BMT, even after relatively low doses of A and XRT. 2) Exercise testing, with assessment of VO_2 , CI, and VAT, noninvasively detects cardiac dysfunction after treatment with A and XRT and is preferable to parameters at rest for the detection of cardiac toxicity in these pts.

CARDIOMYOPATHY IN GLUTARIC ACIDURIA TYPE II
*Kenneth L. Jue, FAAP and Susan Winter, FAAP
Valley Children's Hospital, Fresno, CA

Glutaric aciduria type II (GA II) is an autosomal recessive defect of electron transport flavoprotein. Associated cardiomyopathy has been described in some cases. We report 5 cases (4 female, 1 male) with late onset GA II who presented between 10-36 months of age with severe CHF and cardiomyopathy. Prominent hepatomegaly (4 pts.) and decreased muscle tone and weakness (3 pts.) were present.

EKG showed LVH (3 pts.), RVH (1 pt.), and decreased QRS voltage (1 pt.). Chest x-ray showed prominent cardiomegaly in all cases. Echocardiography demonstrated both dilated (4 pts.) and hypertrophic (1 pt.) forms of cardiomyopathy. Severe LV dysfunction was present in all cases (fractional shortening LV 11-16%). LV diastolic dimension ranged from 30.4 - 65 mm. Mitral regurgitation was observed in all cases.

Initial laboratory studies showed metabolic acidosis (4 pts.), elevated liver enzymes (3 pts.), hyperammonemia (2 pts.), low free carnitine (2 pts.) and increased esterified/free carnitine ratio (3 pts.). Organic acids showed elevated glutaric acid (4 pts.), adipic acid (5 pts.) and ethylmalonic acid (1 pt.) compatible with GA II.

In addition to digoxin, lasix, and captopril, patients received a low fat diet (20% of calories as fat), riboflavin (100 mg B.I.D.) and L-Carnitine (200 mg/kg/day).

Of the 5 cases, 3 have improved cardiac function with persistent cardiomegaly, 1 has undergone cardiac transplantation, and 1 has expired.

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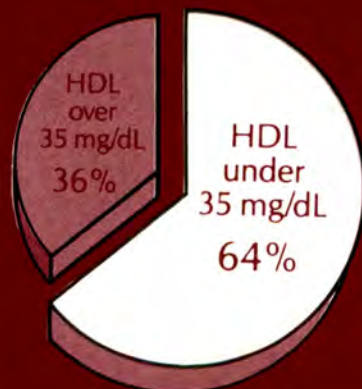
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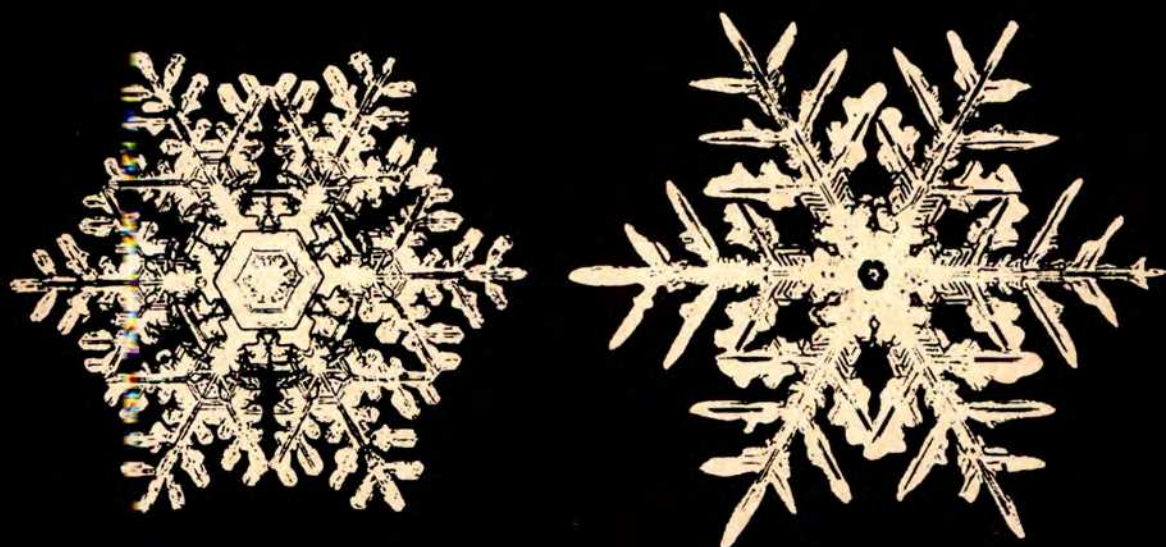
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unknown: Clinically important changes in standard laboratory tests were rarely associated with Lotensin administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of hyponatremia, electrocardiographic changes, leukopenia, eosinophilia, and proteinuria. In U.S. trials, less than 0.5% of patients discontinued treatment because of laboratory abnormalities.

OVERDOSAGE Single oral doses of 3 g/kg benazepril were associated with significant lethality in mice. Rats however, tolerated single oral doses of up to 6 g/kg. Reduced activity was seen at 1 g/kg in mice and at 5 g/kg in rats. Human overdoses of benazepril have not been reported, but the most common manifestation of human benazepril overdose is likely to be hypotension.

Laboratory determinations of serum levels of benazepril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of benazepril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of benazepril and its metabolites. Benazepril can be removed from the body by dialysis, but this intervention should rarely, if ever, be required.

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of benazepril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of benazepril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat benazepril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION The recommended initial dose for patients not receiving a diuretic is 10 mg once-a-day. The usual maintenance dosage range is 20-40 mg per day administered as a single dose or in two equally divided doses. A dose of 80 mg gives an increased response, but experience with this dose is limited. The divided regimen was more effective in controlling trough (pre-dosing) blood pressure than the same dose given as a once-daily regimen. Dosage adjustment should be based on measurement of peak (2-6 hours after dosing) and trough responses. If a once-daily regimen does not give adequate trough response an increase in dosage or divided administration should be considered. If blood pressure is not controlled with Lotensin alone, a diuretic can be added.

Total daily doses above 80 mg have not been evaluated.

Concomitant administration of Lotensin with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium (see PRECAUTIONS).

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of Lotensin. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with Lotensin (see WARNINGS). Then, if blood pressure is not controlled with Lotensin alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg Lotensin should be used to avoid excessive hypotension.

Dosage Adjustment in Renal Impairment

For patients with a creatinine clearance <30 mL/min/1.73 m² (serum creatinine >3 mg/dL), the recommended initial dose is 5 mg Lotensin once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 40 mg.

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CORONARY ARTERY DISEASE**429****Effects of Diltiazem on Long-Term Outcome After Acute Myocardial Infarction in Patients With and Without a History of Systemic Hypertension**

Arthur J. Moss, David Oakes, Michael Rubison, Michael McDermott, Eric Carleen, Shirley Eberly, Mary Brown, and the Multicenter Diltiazem Postinfarction Trial Research Group

The effect of diltiazem on long-term outcome in postinfarction patients with and without a history of hypertension was investigated in 2,466 patients using the Multicenter Diltiazem Postinfarction Trial database. Univariate and multivariate analyses revealed a meaningful reduction in cardiac events in patients with hypertension treated with diltiazem compared with those taking placebo, but little if any effect in patients without hypertension. Most patients with hypertension without pulmonary congestion during the index infarction had a reduction in cardiac events with diltiazem, whereas the reverse was evident in patients with pulmonary congestion.

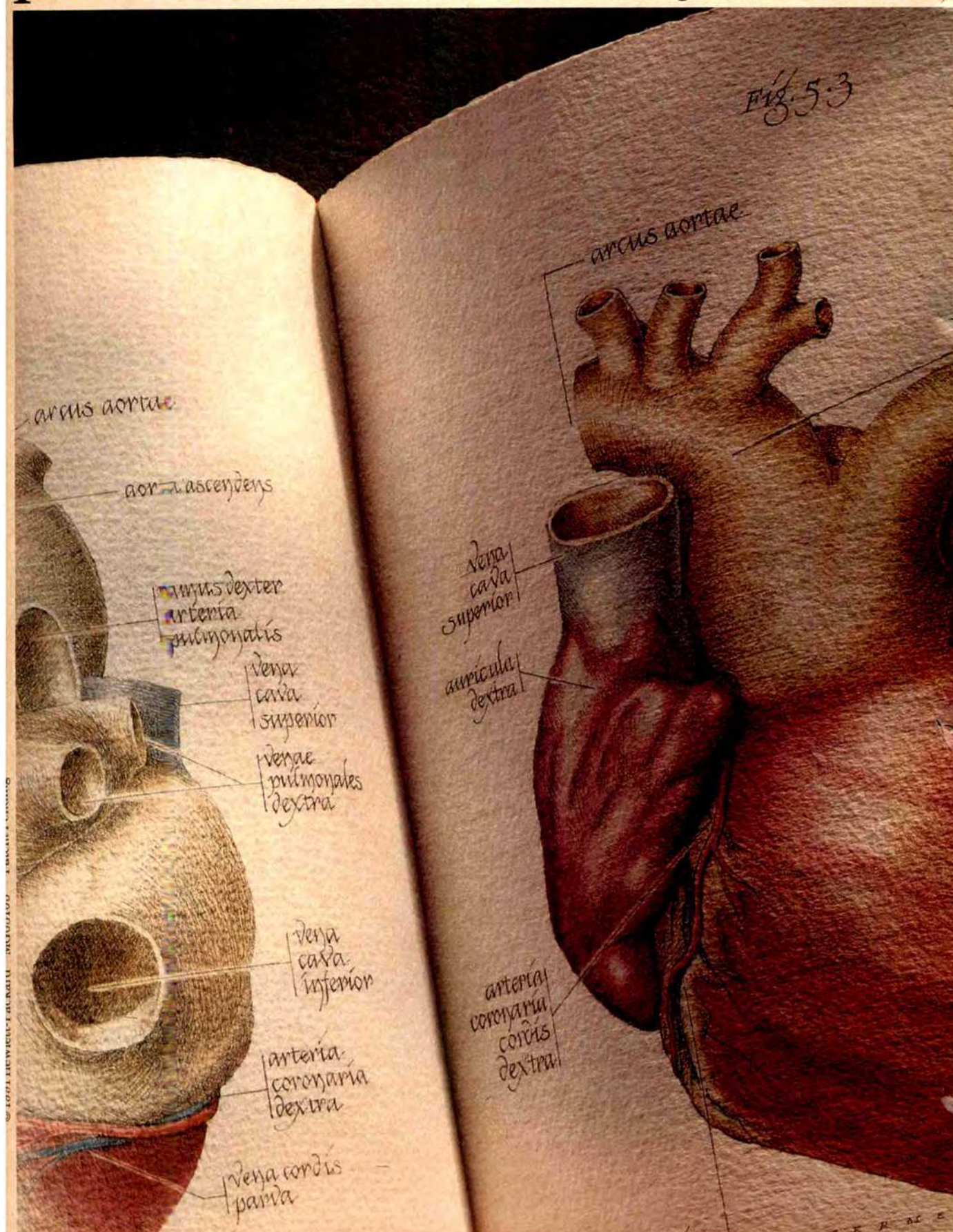
434**Comparison of the Predictive Characteristics of Heart Rate Variability Index and Left Ventricular Ejection Fraction for All-Cause Mortality, Arrhythmic Events and Sudden Death After Acute Myocardial Infarction**

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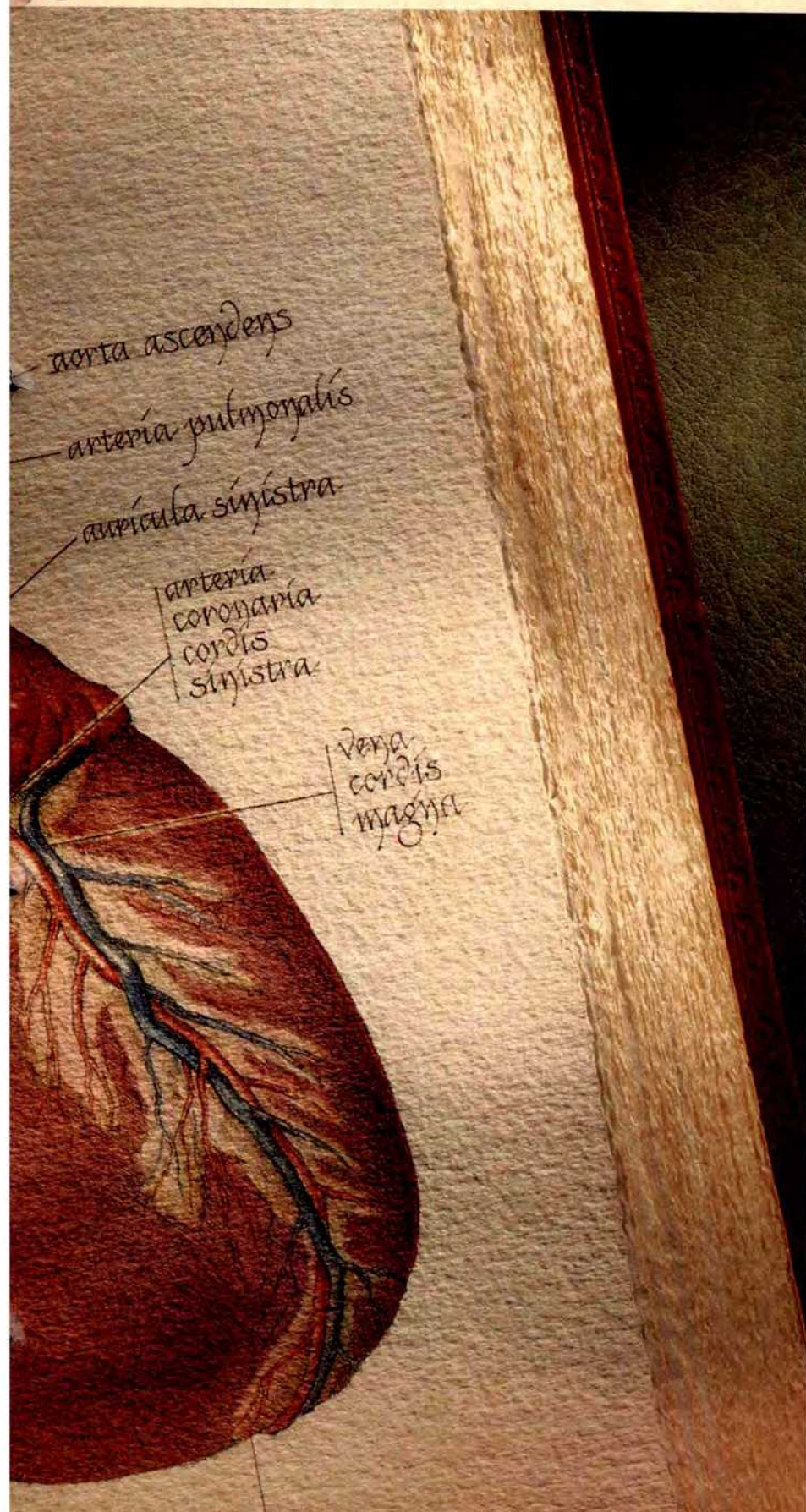
Heart rate (HR) variability index and left ventricular ejection fraction (EF) were compared for the prediction of all-cause mortality, arrhythmic events and sudden death in 385 survivors of acute myocardial infarction. Compared with EF, HR variability index was a better predictor of arrhythmic events and sudden death. However, the combination of HR variability and the left ventricle improved the specificity for predicting all-cause mortality for values of sensitivity <60%; and the same combination improved the specificity for predicting arrhythmic events and sudden death when sensitivity lay between 25 and 75%.

Continued on page A18

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Age-Related Normal Values of Signal-Averaged Electrocardiographic Variables After Acute Myocardial Infarction

Marek Malik, Olusola Odemuyiwa, Jan Poloniecki, Piotr Kulakowski, Thomas Farrell, Anne Staunton, and A. John Camm

This study examined the correlation of standard time domain variables of signal-averaged electrocardiography with age in 328 survivors of acute myocardial infarction and the influence of age on the prediction of postinfarction arrhythmic complication (sudden death or sustained ventricular tachycardia, or both) based on late potential diagnosis. Statistically highly significant correlations ($p \leq 0.00002$) between age and signal-averaged electrocardiographic variables were found: The total duration of signal averaged QRS complexes and duration of the terminal low-amplitude signals increase with increasing age, whereas the mean voltage of the terminal portion of the averaged complexes decreases with increasing age. Compared with patients aged <60 years, the late potential-based stratification of arrhythmic complications after myocardial infarction in patients aged >60 years had lower sensitivity for the same values of specificity and lower specificity for the same values of sensitivity.

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Non-Q- and Q-Wave Infarction After Thrombolytic Therapy with Intravenous Streptokinase for Chest Pain and Anterior ST-Segment Elevation

Lalit Chouhan, Hajar A. Hajar, Thomas George, and Juan Carlos Pomposiello

Seventy-five consecutive patients with chest pain and anterior ST-segment elevation seen within 6 hours of onset of symptoms were treated with intravenous streptokinase. None of the patients had a Q wave on the admission electrocardiogram. After treatment, 43% of the patients had a non-Q-wave type of infarction, whereas 57% developed a Q-wave infarction. At cardiac catheterization performed during hospital stay at comparable intervals after admission, there were no differences between the Q-wave and the non-Q-wave groups with regard to patency of the infarct-related artery or the extent of coronary artery disease. However, those with a non-Q-wave type of infarction had better preserved left ventricular function evaluated at catheterization. It is concluded that thrombolytic therapy when given for chest pain and anterior ST-segment elevation may be preventing development of a Q-wave infarction in a significant number of patients, and the patency rates seen in both the non-Q-wave and the Q-wave infarct groups is high with better preserved left ventricular function in the non-Q-wave group.

451

Effects of Urokinase and Heparin on Minimal Cross-Sectional Area of the Culprit Narrowing in Unstable Angina Pectoris

Mara Sansa, Carmelo Cernigliaro, Andrea Campi, and Ignazio Simonetti

The effects of urokinase and heparin were prospectively investigated in 43 patients with unstable angina. After baseline angiography, patients were

Continued on page A21

randomized to: urokinase (1,000,000 U intravenous bolus) followed by heparin 3 hours later (group I); heparin (10,000 U) followed by continuous infusion (group II); conventional therapy (group III). Angiography was repeated at 1 hour and 8 days. In group I, the culprit narrowing was $0.84 \pm 0.48 \text{ mm}^2$ at baseline, $0.94 \pm 0.49 \text{ mm}^2$ at 1 hour ($p < 0.05$) and $1.00 \pm 0.51 \text{ mm}^2$ at 8 days ($p < 0.01$ vs baseline). In group II, the culprit narrowing was $0.64 \pm 0.39 \text{ mm}^2$ at baseline, $0.67 \pm 0.37 \text{ mm}^2$ at 1 hour ($p = \text{not significant}$) and $0.79 \pm 0.48 \text{ mm}^2$ ($p < 0.01$ versus baseline). In group III no significant changes occurred. Thus, both urokinase and heparin improved lesion geometry. The effect occurred earlier with urokinase than with heparin.

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Twenty-Four-Hour Activity of Felodipine Extended Release in Chronic Stable Angina Pectoris

Gino Santoro, Stefano Savonitto, Vito Di Bello, Daniele Alberti, and Costantino Giusti

The antiischemic activity and duration of action of the calcium antagonist felodipine was investigated in 15 patients with chronic stable angina. Five- and 10-mg once-daily doses of the extended release formulation of felodipine were administered for 7 days in a placebo-controlled crossover study. Exercise tests were repeated 4 and 24 hours after last drug administration. Both doses increased mean time to 1 mm of ST depression and rate-pressure product at 24 hours, when 11 patients with 10 mg and 5 patients with 5 mg had an increase in time to 1-mm ST depression $\geq 15\%$ compared with exercise time during the placebo test. At 4 hours, the 2 felodipine doses had similar efficacy, while at 24 hours the 10-mg dose was more effective. We conclude that a once-daily administration of felodipine extended release provides antiischemic activity for 24 hours in stable exercise-induced angina. Because no differences in tolerability were observed between the 5- and 10-mg doses, and the 10-mg dose was more effective 24 hours after dosing, the latter is preferred for once-daily treatment.

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Ridogrel in the Setting of Percutaneous Transluminal Coronary Angioplasty

Carl Timmermans, Matty Vrolix, Johan Vanhaecke, Francis Stammen, Jan Piessens, Els Vercammen, and Hilaire De Geest

Ridogrel was administered to 32 patients undergoing coronary angioplasty. The drug effectively eliminated thromboxane B_2 from the serum, with a concomitant increase in serum 6-keto-prostaglandin $F_{1\alpha}$. The combination with heparin appears to be reasonably safe. Further investigation of the effectiveness of ridogrel in preventing early acute reocclusion and subacute restenosis after coronary angioplasty is warranted.

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Use of a Morphologic Classification to Predict Clinical Outcome After Dissection from Coronary Angioplasty

Michael S. Huber, Jodi Fishman Mooney, James Madison, and Michael R. Mooney

Procedure-related dissections during percutaneous transluminal coronary angiography were classified according to a preexisting National Heart, Lung, and Blood Institute schema; the different classes were then correlated with outcome. Five hundred and forty-three patients with type B dissections had high success rates (93.7%) similar to those in patients without dissection. Overall complications in this group were low and compared favorably with procedures not associated with dissections. One hundred forty-eight patients with type C to F dissections had significantly increased ($p < 0.0005$) acute complications and lower overall success rates (37.8%). Classifying morphology by this schema can help direct effective therapy after dissection.

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Noninvasive Identification of Significant Narrowing of the Left Main Coronary Artery by Dipyridamole Thallium Scintigraphy

Taishiro Chikamori, Yoshinori L. Doi, Yoshihiro Yonezawa, Mitsutoshi Yamada, Hiromi Seo, and Toshio Ozawa

To evaluate the usefulness of dipyridamole thallium scintigraphy with low-level exercise for the identification of left main (LM) coronary artery disease (CAD), 466 consecutive patients with CAD in whom 38 had LMCAD were studied. The LM scintigraphic pattern had a sensitivity of 67% and a specificity of 91% for LMCAD without right CAD versus CAD without LMCAD, and sensitivity of 10% and specificity of 91% for LM and right CAD versus CAD without LMCAD. The combination of clinical markers of ischemia during dipyridamole loading and scintigraphic findings of severe CAD best identified patients with LM and right CAD (sensitivity 72%, specificity 80%). These results indicate that the LM scintigraphic pattern is specific and sensitive for LMCAD without right CAD. In LM and right CAD, the predictability of this finding is low, but the addition of clinical markers of ischemia during dipyridamole loading facilitates better identification.

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Evaluation of Dipyridamole-Doppler Echocardiography for Detection of Myocardial Ischemia and Coronary Artery Disease

Peter Mazeika, Petros Nihoyannopoulos, Jayshree Joshi, and Celia M. Oakley

Thirty-four patients were studied using pulsed Doppler interrogation of left ventricular filling and ejection during dipyridamole stress. Twelve patients had normal coronary arteries (group 1), and the remaining patients with significant coronary artery disease (CAD) were divided into groups 2 ($n = 11$) and 3 ($n = 11$). Dipyridamole-induced ischemia developed only in Group 2 patients. Changes in peak early filling velocity, peak atrial velocity, their ratio, and ejection peak velocity and mean acceleration in the 3 groups were similar. Comparisons between normal

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patients and those with CAD and between groups 2 and 3 revealed no significant differences in the effects on any variable. Dipyridamole-Doppler echocardiography is insensitive for detection of CAD and appears unable to identify myocardial ischemia unless this is severe. Hemodynamic changes and compensatory wall motion induced by dipyridamole may explain these findings.

485**Pronounced Reduction of Aortic Flow Velocity and Acceleration During Heavy Isometric Exercise in Coronary Artery Disease**

Enrique Z. Fisman, Efraim Ben-Ari, Amos Pines, Yaacov Drory, Robert J. Shiner, Michael Motro, and Jan J. Kellermann

Doppler-derived parameters of aortic flow were examined during heavy isometric exercise in 48 documented men with coronary artery disease (CAD) and 48 gender- and age-matched healthy control subjects. A significant decrease was documented in peak flow velocity, flow velocity integral, mean acceleration, and stroke volume and cardiac indexes; acceleration time increased. In most of the indexes, the directional changes were similar for both groups, but the differences compared with the rest values were greater in the group with CAD, and especially in the patients presenting with 3-vessel disease. In conclusion, isometric exercise results in marked changes in aortic flow patterns both in normal subjects and in patients with CAD. Exercise-induced changes in peak flow velocity and mean acceleration were found to differ significantly between the groups, and the degree of reduction in their values directly related to the extent of CAD.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES**492****Usefulness of Excitable Gap and Pattern of Resetting in Atrial Flutter for Determining Reentry Circuit Location**

Paolo Della Bella, Giancarlo Marenzi, Claudio Tondo, Daniela Cardinale, Francesco Giraldi, Gianfranco Lauri, and Maurizio Guazzi

The purpose of this study was to localize sites suitable for temporary or permanent interruption of the reentry circuit in atrial flutter. The width of the excitable gap, the poststimulation cycle and the pattern of reset after a premature stimulus were analyzed in 18 patients during type I atrial flutter at multiple atrial sites. The excitable gap was shorter at the coronary sinus (33 ± 8 ms) and high right atrium (30 ± 10 ms) than at the posterior (43 ± 9 ms) and septal right atrium (45 ± 11 ms). The poststimulation cycle was shorter at the posterior (6 ± 7 ms) and septal right atrium (5 ± 7 ms) than at the coronary sinus (35 ± 9 ms) and high (23 ± 10 ms) and low right atrium (15 ± 9 ms). A flat pattern of resetting occurred more frequently at the septal (18 of 18 patients) and posterior right atrium (15 of 18) than at the low (8 of 18) and high right atrium (2 of 17), and was never observed at the coronary sinus. The relation between shortest poststimulation cycle, flat pattern of resetting and widest excitable gap was consistently observed at the septal and posterior right atrium.

Atrial flutter was successfully terminated by overdrive pacing in 15 of 18 patients and termination was more easily obtained from the septal and posterior right atrium. The described criteria might be useful to improve efficacy in the electric termination of atrial flutter and for ablative therapy.

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Effects of Exercise on Heart Rate, QT, QTc and QT/QS2 in the Romano-Ward Inherited Long QT Syndrome

G. Michael Vincent, Deepak Jaiswal, and Katherine W. Timothy

Exercise was performed in 27 subjects with Romano-Ward long QT interval and 27 normal controls to evaluate sympathetic control of heart rate and QT cycle length relationships, and to evaluate the diagnostic usefulness of measurements during exercise. Heart rate was lower in subjects with Romano-Ward syndrome during moderate and maximal exercise (151.6 vs 169.6 beats/min, $p = 0.4$; 155.7 vs 185.1 beats/min, $p = 0.001$, respectively). The QT of subjects with Romano-Ward syndrome failed to shorten normally, and QTc increased; however, it decreased in normals. Resting QT/QS2 ratio in patients with Romano-Ward syndrome was higher (1.12) than in normals (0.92), $p = 0.001$. During exercise, QT/QS2 in Romano-Ward subjects increased by 30% (1.12 to 1.45) compared with 15% in normals (0.92 to 1.07). Romano-Ward subjects have an abnormal heart rate and QT response to exercise. The QT/QS2 at rest and the QT/QS2 and QT response to exercise may have diagnostic utility.

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Improved Specificity of Myocardial Thallium-201 Single-Photon Emission Computed Tomography in Patients with Left Bundle Branch Block by Dipyridamole

Robert J. Burns, Luke Galligan, Linda M. Wright, Samih Lawand, Ronald J. Burke, and Peter J. Gladstone

Sixteen patients with left bundle branch block underwent exercise and dipyridamole thallium-201 single-photon emission computed tomography and coronary angiography within 3 months. Sensitivity for detection of left anterior descending coronary artery disease was 0.83 for exercise and 1.00 for dipyridamole. Specificity was 0.30 (visual) or 0.20 (quantitative analysis) for exercise and 0.80 (visual) or 0.90 (quantitative) for dipyridamole ($p < 0.05$). Dipyridamole combined with quantitative analysis also improved specificity for detecting coronary artery disease overall ($p < 0.01$). These results support use of pharmacologic vasodilation rather than exercise for diagnosis of coronary artery disease by myocardial perfusion scintigraphy in patients with left bundle branch block.

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SYSTEMIC HYPERTENSION

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Hemodynamic Effects of Celiprolol in Essential Hypertension

Edward D. Frohlich, Reinhard Ketelhut, Ulrich R. Kaesser, Christoph J. Losem, and Franz H. Messerli

Hemodynamic and humoral effects of the new β_1 antagonist, β_2 agonist, celiprolol, were compared with those of atenolol in 12 patients with essential hypertension. Unlike early β blockers, celiprolol (intravenously) immediately produced a dose-dependent decrease in arterial pressure and total peripheral resistance without reducing heart rate or cardiac output. These effects persisted with short-term treatment; unlike atenolol, this was associated with a reduced total peripheral resistance. Splanchnic and forearm vascular resistances were reduced with celiprolol, and neither agent altered renal blood flow. These effects may be explained by the different pharmacologic actions of celiprolol.

METHODS

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Use of Valsalva Maneuver to Unmask Left Ventricular Diastolic Function Abnormalities by Doppler Echocardiography in Patients with Coronary Artery Disease or Systemic Hypertension

Jean G. Dumesnil, Gertie Gaudreault, George N. Honos, and John G. Kingma, Jr.

The effect of the Valsalva maneuver on Doppler transmitral flow velocity profile was evaluated in 28 patients without heart disease and 94 patients with evidence of ischemic heart disease or hypertension. E/A ratio did not change significantly during Valsalva and remained ≥ 1.0 in all patients but 1 without disease, whereas it was ≥ 1.0 at rest and became < 1.0 during Valsalva in 33 patients with disease. Prevalence, specificity and positive predictive value of E/A < 1.0 in patients with disease were 31, 100 and 100% at rest and 66, 96 and 98% during Valsalva. The ability to correctly classify patients with and without disease on the basis of E/A < 0.1 was 47% at rest and 73% during Valsalva. This study shows that the Valsalva maneuver is an easy means of acutely reducing left atrial pressures during Doppler echocardiography and of unmasking otherwise unsuspected diastolic function abnormalities.

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EMINASE[®]

ANISTREPLASE 30U

INDICATIONS AND USAGE: EMINASE[®] ANISTREPLASE is indicated for use in the management of acute myocardial infarction (AMI) in adults, for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, EMINASE[®]

is contraindicated in the following situations: ■ active internal bleeding ■ history of cerebrovascular accident ■ recent (within 2 months) intracranial or intraspinal surgery or trauma (see WARNINGS) ■ intracranial neoplasm, arteriovenous malformation, or aneurysm ■ known bleeding diathesis ■ severe, uncontrolled hypertension. EMINASE[®] should not be administered to patients having experienced severe allergic reactions to either this product or Streptokinase.

WARNINGS: Bleeding: (See ADVERSE REACTIONS) The most common complication associated with EMINASE[®] therapy is bleeding. The types of bleeding associated with thrombolytic therapy can be divided into two broad categories: 1. Internal bleeding involving the gastrointestinal tract, genitourinary tract, retroperitoneal, ocular, or intracranial sites. 2. Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention). The concomitant use of heparin anticoagulation may contribute to the bleeding. Some of the hemorrhagic episodes occurred one or more days after the effects of EMINASE[®] had dissipated, but while heparin therapy was continuing. As fibrin is lysed during EMINASE[®] therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites). Intramuscular injections and nonessential handling of the patient should be avoided during treatment with EMINASE[®]. Venipunctures should be performed carefully and only as required. Should an arterial puncture be necessary following administration of EMINASE[®], it is preferable to use an upper-extremity vessel that is accessible to manual compression. A pressure dressing should be applied, and the puncture site should be checked frequently for evidence of bleeding. Each patient being considered for therapy with EMINASE[®] should be carefully evaluated and anticipated benefits should be weighed against potential risks associated with therapy. In the following conditions, the risks of EMINASE[®] therapy may be increased and should be weighed against the anticipated benefits: ■ recent (within 10 days) major surgery (e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of non-compressible vessels) ■ cerebrovascular disease ■ recent gastrointestinal or genitourinary bleeding (within 10 days) ■ recent trauma (within 10 days) including cardiopulmonary resuscitation ■ hypertension: systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg ■ high likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation) ■ subacute bacterial endocarditis ■ acute pericarditis ■ hemostatic defects including those secondary to severe hepatic or renal disease ■ pregnancy ■ age >75 years (Use of EMINASE[®] in patients over 75 years old has not been adequately studied.) ■ diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions ■ septic thrombophlebitis or occluded AV cannula at seriously infected site ■ patients currently receiving oral anticoagulants (e.g., warfarin sodium) ■ any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias: Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when injections of EMINASE[®] are administered.

Hypotension: Hypotension, sometimes severe, not secondary to bleeding or anaphylaxis, has occasionally been observed soon after intravenous EMINASE[®] administration. Patients should be monitored closely and, should symptomatic or alarming hypotension occur, appropriate symptomatic treatment should be administered.

PRECAUTIONS: General: Standard management of myocardial infarction should be implemented concomitantly with EMINASE[®] treatment. Invasive procedures should be minimized (see WARNINGS). Anaphylactoid reactions have rarely been reported in patients who received EMINASE[®]. Accordingly, adequate treatment provisions such as epinephrine should be available for immediate use.

Readministration: Because of the increased likelihood of resistance due to antistreptokinase antibody, EMINASE[®] may not be as effective if administered more than 5 days after prior EMINASE[®] or Streptokinase therapy or streptococcal infection, particularly between 5 days and 6 months. Increased antistreptokinase antibody levels between 5 days and 6 months after EMINASE[®] or Streptokinase administration may also increase the risk of allergic reactions. Repeated administration of EMINASE[®] within one week of the initial dose has occurred in a small number of patients treated for AMI and non-AMI conditions. The incidence of hematomas/bruising was somewhat greater in those patients who received repeat doses of EMINASE[®] but otherwise the adverse event profile was similar to those who received one dose.

Laboratory Tests: Intravenous administration of EMINASE[®] will cause marked decreases in plasminogen and fibrinogen and increases in thrombin time (TT), activated partial thromboplastin time (APTT), and prothrombin time (PT). Results of coagulation tests and/or measures of fibrinolytic activity performed during EMINASE[®] therapy may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. EMINASE[®], when present in blood in pharmacologic concentrations, remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (2000 to 3000 KIU/mL) can, to some extent, mitigate this phenomenon.

Drug Interactions: The interaction of EMINASE[®] with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as aspirin and dipyridamole) may increase the risk of bleeding if administered prior to EMINASE[®] therapy.

Use of Anticoagulants: EMINASE[®] alone or in combination with antiplatelet agents and anticoagulants may cause bleeding complications. Therefore, careful monitoring is advised, especially at arterial puncture sites. In clinical studies, a majority of patients treated received anticoagulant therapy postdosing with EMINASE[®] during their hospital stay and a minority received heparin pretreatment with EMINASE[®]. The use of antiplatelet agents increased the incidence of bleeding events similarly in patients treated with EMINASE[®] or nonthrombolytic therapy. There was no evidence of a synergistic effect of combined EMINASE[®] and antiplatelet agents on bleeding events. In addition, there was no difference in the incidence of hemorrhagic CVA's in EMINASE[®] treated patients who did or did not receive aspirin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Studies to determine mutagenicity and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested.

References

1. Anderson JL, Sorensen SG, Karagounis L, et al. A double-blind, randomized comparison of anistreplase and alteplase in acute myocardial infarction: coronary patency results from the TEAM-3 study. *J Am Coll Cardiol*. 1991;17(suppl A):152A, and data on file, SmithKline Beecham Pharmaceuticals.
2. Machecourt J, Cassagnes J, Bassand JP, et al. Results of a randomized trial comparing APSAC and rPA for the preservation of left ventricular function after acute myocardial infarction. *J Am Coll Cardiol*. 1990;15:64A.

Pregnancy (Category C): Animal reproduction studies have not been conducted with EMINASE[®]. It is also not known whether EMINASE[®] can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. EMINASE[®] should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether EMINASE[®] is excreted in human milk. Because many drugs are excreted in human milk, the physician should decide whether the patient should discontinue nursing or if to receive EMINASE[®].

Pediatric Use: Safety and effectiveness of EMINASE[®] in children have not been established.

ADVERSE REACTIONS: Bleeding: The incidence of bleeding (major or minor) varied widely from study to study and may depend on the use of arterial catheterization and other invasive procedures, patient population, and concomitant therapy. The overall incidence of bleeding in patients treated with EMINASE[®] in clinical trials (n=500) was 14.6%, with nonpuncture-site bleeding occurring in 10.2% and puncture-site bleeding occurring in 5.7% of patients. Bleeding at the puncture site occurred more frequently in clinical trials in which the patients underwent coronary catheterization (13.3%, n=637) compared with those who did not (3.0%, n=2023). The incidence of presumed intracranial bleeding within 7 days postdosing with EMINASE[®] was 0.57% (n=5275); 0.34% of confirmed hemorrhagic; 0.23% etiology not confirmed) compared to 0.16% (n=1249) after nonthrombolytic therapy. In the AIMS trial the overall incidence of bleeding in patients treated with EMINASE[®] was 14.8% compared to 3.8% for placebo. The incidence of specific bleeding events was:

Type of Bleeding	EMINASE [®] (n=500)	Placebo (n=50)
Puncture site	4.6%	<1%
Nonpuncture site hematoma	2.8%	<1%
Hematuria/Genitourinary	2.4%	<1%
Hemoptysis	2.2%	<1%
Gastrointestinal hemorrhage	2.0%	1.4%
Intracranial	1.0%	<1%
Gum/Mouth Hemorrhage	1.0%	0
Epistaxis	<1%	<1%
Anemia	<1%	<1%
Eye Hemorrhage	<1%	<1%
Hemorrhage (unspecified)	<1%	0

In this study there was no difference between EMINASE[®] and placebo in the incidence of major bleeding events. Should serious bleeding (not controlled by local pressure) occur in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial), any concomitant heparin should be terminated immediately and the administration of protamine to reverse heparinization should be considered. If necessary, the bleeding tendency can be reversed with appropriate replacement therapy. Minor bleeding can be anticipated mainly at invaded or disturbed sites. If such bleeding occurs, local measures should be taken to control the bleeding (see WARNINGS).

Cardiovascular: The most frequently reported adverse experiences in EMINASE[®] clinical trials (n=5275) were arrhythmia/conduction disorders which were reported in 38% of patients treated with EMINASE[®] and 46% of nonthrombolytic control patients. Hypotension occurred in 10.4% of patients treated with EMINASE[®] compared to 7.9% for patients who received nonthrombolytic treatment (see WARNINGS).

Allergic-type Reactions: Anaphylactic and anaphylactoid reactions have been observed rarely (0.2%) in patients treated with EMINASE[®] and are similar in incidence to Streptokinase (0.1% anaphylactic shock in one study). These include symptoms such as bronchospasm or angioedema. Other milder or delayed effects such as urticaria, itching, flushing, rashes, and eosinophilia have been occasionally observed. A delayed purpuric rash appearing one to two weeks after treatment has been reported in 0.3% of patients. The rash may also be associated with arthralgia, ankle edema, gastrointestinal symptoms, mild hematuria, and mild proteinuria. This syndrome was self-limiting and without long-term sequelae.

Risk of Viral Transmission: Six batches of EMINASE[®] (five different batches of Lys-Plasminogen) were used in clinical trials designed specifically to monitor possible hepatitis non-A, non-B transmission. No case of hepatitis was diagnosed in patients receiving EMINASE[®]. Lys-Plasminogen is derived from human plasma obtained from FDA approved sources and tested for absence of viral contamination, including human immunodeficiency virus type-1 (HIV-1) and hepatitis B surface antigen. The manufacturing process includes a vapor-heat treatment step for inactivation of viruses. The entire manufacturing process has also been validated to yield a cumulative reduction of $\geq 10^4$ fold HIV-1 infectious particles, i.e., $\geq 10^6$ infectious particles removed by vapor-heat treatment and a cumulative total of $\geq 10^5$ infectious particles removed by the various steps in the purification process.

Causal Relationship Unknown: Since the following experiences may also be associated with AMI or other therapy, the causal relationship to EMINASE[®] administration is unknown. The following adverse experiences were infrequently (<10%) reported in clinical trials: **Body as a Whole**—chills, fever, headache, shock; **Cardiovascular**—cardiac rupture, chest pain, emboli; **Dermatology**—purpura, sweating; **Gastrointestinal**—nausea and/or vomiting; **Hemic and Lymphatic**—thrombocytopenia; **Metabolic and Nutritional**—elevated transaminase levels; **Musculoskeletal**—arthralgia; **Nervous**—agitation, dizziness, paresthesia, tremor, vertigo; **Respiratory**—dyspnea, lung edema.

DOSEAGE AND ADMINISTRATION: Administer EMINASE[®] as soon as possible after the onset of symptoms. The recommended dose is 30 units of EMINASE[®] administered only by intravenous injection over 2 to 5 minutes into an intravenous line or vein.

Reconstitution: 1. Slowly add 5 mL of Sterile Water for Injection, U.S.P. by directing the stream of fluid against the side of the vial. 2. Gently roll the vial, mixing the dry powder and fluid. **Do not shake.** Try to minimize foaming. 3. The reconstituted preparation is a colorless to pale yellow transparent solution. Before administration, the product should be visually inspected for particulate matter and discoloration. 4. Withdraw the entire contents of the vial. 5. The reconstituted solution should not be further diluted before administration or added to any infusion fluids. No other medications should be added to the vial or syringe containing EMINASE[®]. 6. If EMINASE[®] is not administered within 30 minutes of reconstitution, it should be discarded.

HOW SUPPLIED: EMINASE[®] is supplied as a sterile, lyophilized powder in 30-unit vials. NDC 57294-030-20.

Storage: Store lyophilized EMINASE[®] between 2-8°C (36-46°F). Do not use beyond the expiration date printed on the vial.

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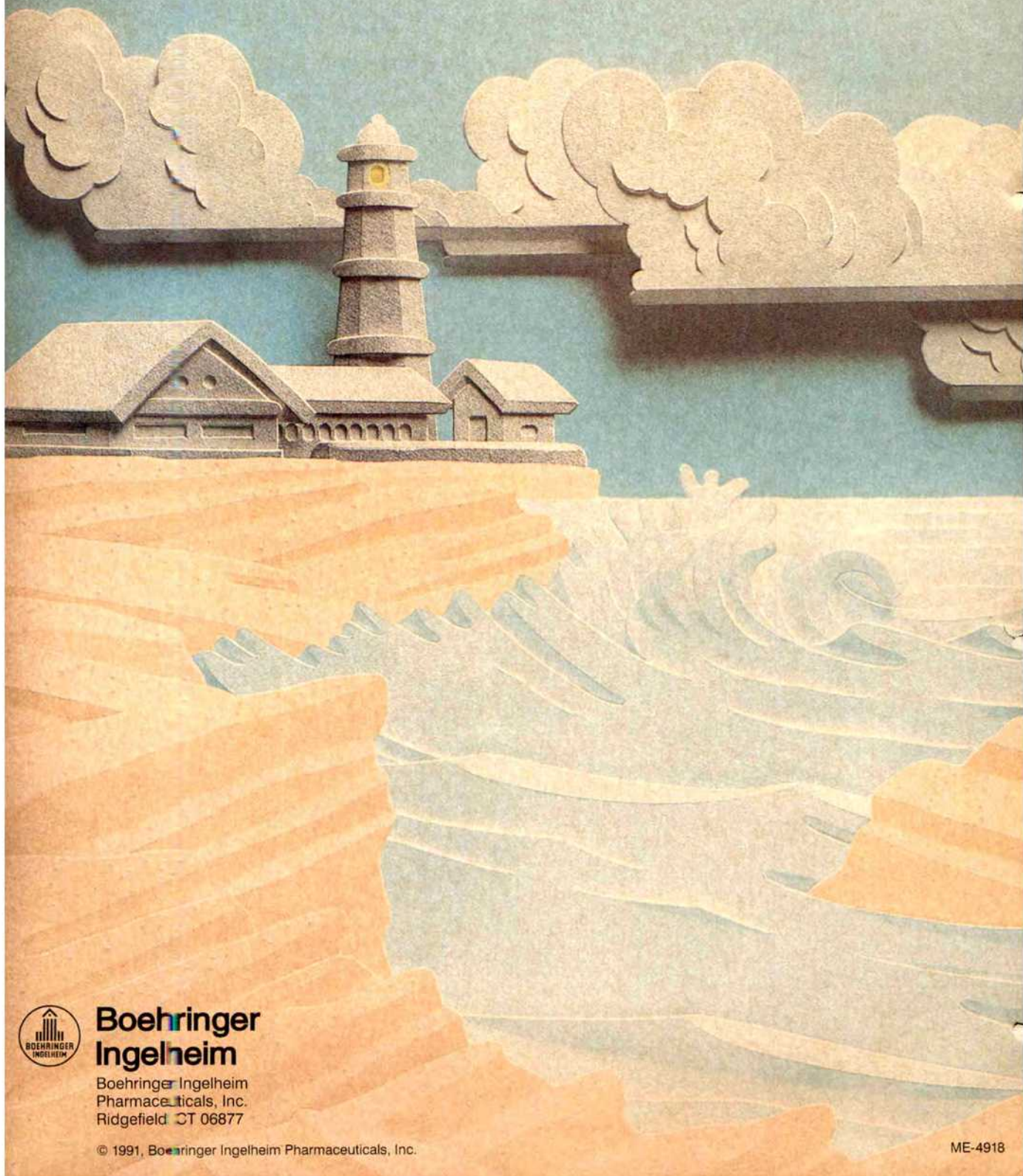
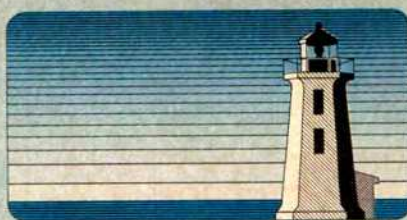
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ME-4918

Effects of Diltiazem on Long-Term Outcome After Acute Myocardial Infarction in Patients With and Without a History of Systemic Hypertension

Arthur J. Moss, MD, David Oakes, PhD, Michael Rubison, PhD, Michael McDermott, PhD, Eric Carleen, MA, Shirley Eberly, MS, Mary Brown, MS, and the Multicenter Diltiazem Postinfarction Trial Research Group*

The effect of diltiazem on long-term outcome in patients with acute myocardial infarction with and without a history of systemic hypertension was investigated in 2,466 patients using the Multicenter Diltiazem Postinfarction Trial database. The baseline variables were comparable in the diltiazem and placebo-treated patients within the groups with and without hypertension. The initial 60-mg dose of diltiazem was associated with a significant ($p < 0.001$) but modest (3%) reduction in blood pressure and heart rate in both groups with and without hypertension. Univariate and multivariate analyses revealed a meaningful overall reduction in first recurrent cardiac events (cardiac death or nonfatal reinfarction, whichever occurred first) and cardiac death in patients with hypertension treated with diltiazem compared with results in those treated with placebo. Similar effects were not observed in patients without a history of hypertension. When first recurrent cardiac events were used as the end point, the diltiazem:placebo hazard ratio

(95% confidence limits) was 0.77 (0.58, 1.01) for the total hypertension group, and 0.67 (0.47, 0.96) and 1.32 (0.83, 2.10) for patients with hypertension with and without pulmonary congestion during the acute infarction, respectively. Similar results were observed using cardiac death as the end point. Beta blockers had a negligible effect on the hypertension-diltiazem relation. These findings suggest that diltiazem may exert a long-term beneficial effect in most patients with hypertension who do not have pulmonary congestion during an acute infarction, and a detrimental effect in the minority who have pulmonary congestion.

(Am J Cardiol 1991;68:429-433)

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The primary findings from the Multicenter Diltiazem Postinfarction Trial (MDPIT) have recently been reported.¹ Treatment with diltiazem exerted no significant overall effect on mortality or first recurrent cardiac events (cardiac death or nonfatal reinfarction, whichever occurred first) during long-term follow-up. The neutral overall effect concealed a significant bidirectional interaction between diltiazem and the presence or absence of roentgenographic evidence of pulmonary congestion.¹ There was a diltiazem-related reduction in the cardiac event rate in most patients without evidence of left ventricular dysfunction and an increase in the rate of such events in the minority of patients with left ventricular dysfunction.²

Systemic hypertension is due in large part to increased arteriolar tone, and diltiazem as well as several other calcium antagonists, which induce systemic arterial vasodilation, are effective antihyperten-

sive agents.³⁻⁵ Many patients who sustain a myocardial infarction have preexisting hypertension, and it is reasonable to hypothesize that calcium antagonists, like β blockers, may be particularly efficacious in this group of patients. The primary purpose of this report was to use the MDPIT database to examine the effects of diltiazem on long-term outcome in patients with and without a history of hypertension preceding their myocardial infarction. A secondary purpose was to examine the consistency of the bidirectional interaction between diltiazem and left ventricular dysfunction across subgroups with and without hypertension.

METHODS

Population: The design, organization, patient recruitment, data acquisition, clinical follow-up and data management aspects of MDPIT have previously been reported.¹ The reported analyses utilize the analytic database released April 1, 1988.

The total MDPIT population includes 2,466 patients, 25 to 75 years of age, randomized to placebo ($n = 1,234$) or diltiazem ($n = 1,232$) therapy after a documented acute myocardial infarction and followed for 12 to 52 months; the average duration of follow-up was 25 months. The standard dose of diltiazem was 60 mg 4 times daily, but the physician-investigator could reduce the dose as deemed necessary. At 2 years of follow-up, 63% of both the placebo- and diltiazem-treated patients were taking trial medication.

Definition of hypertension: Patients were identified as having a history of hypertension if specific antihypertensive therapy had been prescribed by a physician at any time before the index acute myocardial infarction. This definition was specified in a manual of operations written before initiation of MDPIT. Blood pressure at the time of enrollment was not used as a criterion for hypertension. In all, 942 patients met the aforementioned definition of hypertension, 38% of the total MDPIT population, and 1,524 patients were categorized as not having a history of hypertension.

Variables: Routine clinical variables obtained at baseline were defined in the primary manuscript.¹ Pulmonary congestion on chest roentgenogram during the index infarction was classified as a 2-level variable (no congestion vs any congestion). Beta blocker use (yes, no) was determined at the time of randomization, and the percentage of patients taking β blockers at 1-year follow-up (55%) was similar to that found at randomization (54%). Concurrent therapy exclusive of calcium antagonists was not controlled and was left to the patient's personal physician.

End points: The end points of interest in the current analyses were cardiac death and first recurrent cardiac event (cardiac death or nonfatal reinfarction, whichever

occurred first). All deaths and nonfatal reinfarctions were categorized by independent end-point subcommittees according to written criteria without knowledge of the patient's assigned trial medication.

Statistical considerations: Life-table methods (Kaplan-Meier) were utilized to account for variations in follow-up duration.⁶ Treatment effects were assessed separately for cardiac death and first recurrent cardiac event end points by the calculations of hazard ratios (diltiazem:placebo) from the Cox proportional-hazards regression model.⁷ A lower event rate in patients taking diltiazem than in patients taking placebo would lead to a hazard ratio less than unity, and vice-versa. The statistical significance of a particular comparison can be gauged from the corresponding confidence interval; event rates between the diltiazem and placebo groups differ significantly at the $p < 0.05$ level (2-sided) if the confidence interval for the corresponding hazard ratio does not include the value of unity. Analyses were performed using the program BMDP2L,⁸ with 38 enrolling hospitals entered as stratification factors, and the 3 design variables (use of β blockers at randomization, randomization within 5 days of the index infarction, and New York Heart Association functional class I vs II to IV) were entered as binary covariates. Analyses were performed separately to evaluate: (1) the 2-factor treatment-hypertension interaction; (2) the 3-factor treatment-hypertension-pulmonary congestion interaction; and (3) the 3-factor treatment-hypertension- β blocker interaction.

RESULTS

Comparability of treatment groups: The baseline characteristics of patients with and without a history of hypertension subdivided by placebo and diltiazem treatment are presented in Table I. The baseline variables were comparable in the 2 treatment subsets within groups with and without hypertension. There was no major imbalance between the treatment subsets of any variable reflecting the severity of the myocardial disease.

Initial hemodynamic response to diltiazem: The blood pressure and heart rate were measured before and 2 hours after the initial oral dose of trial medication (placebo, diltiazem 60 mg) (Table II). The baseline (before) blood pressure and heart rate parameters were within normal limits in those with and without a history of hypertension, but the levels of these parameters were significantly higher in those with than without a history of hypertension. With diltiazem, systolic blood pressure declined 3 to 4 mm Hg, diastolic blood pressure 2 mm Hg, heart rate 2 beats/min, and double product (systolic blood pressure \times heart rate) 4 to 5 U/s. Each of these reductions with diltiazem was highly

TABLE I Baseline Characteristics of the Population

Characteristics	No Hypertension		Hypertension	
	Placebo (n = 762)	Diltiazem (n = 760)	Placebo (n = 471)	Diltiazem (n = 471)
Mean age (years)	57 ± 10	57 ± 10	60 ± 9	60 ± 9
< 60	405 (53)	418 (55)	201 (43)	198 (42)
60–69	272 (36)	256 (34)	202 (43)	201 (43)
70–75	85 (11)	86 (11)	68 (14)	72 (15)
Men	643 (84)	639 (84)	333 (71)	354 (75)
Cardiac history				
Previous myocardial infarction	135 (18)	169 (22)	122 (26)	98 (21)
NYHA II–IV*	108 (14)	129 (17)	112 (24)	101 (21)
Coronary bypass surgery	40 (5)	49 (6)	26 (6)	30 (6)
Insulin-dependent diabetes	55 (7)	44 (6)	51 (11)	63 (13)
Cigarette smoking	401 (53)	429 (57)	199 (42)	175 (38)
Cardiac findings				
Shock	19 (2)	24 (3)	13 (3)	12 (3)
> Bibasilar rales	40 (5)	41 (5)	38 (8)	34 (7)
Pulmonary congestion†	133 (18)	145 (20)	114 (25)	97 (21)
Creatine kinase (> 1,000 U)	395 (52)	396 (52)	206 (44)	209 (44)
Blood urea nitrogen (> 35 mg/dl)	47 (6)	29 (4)	46 (10)	50 (11)
Systolic blood pressure (< 100 mm Hg)	33 (4)	35 (5)	17 (4)	14 (3)
Type and location of acute infarction				
Anterolateral Q-wave	238 (31)	243 (32)	149 (32)	144 (31)
Inferoposterior Q-wave	315 (41)	315 (41)	167 (35)	185 (40)
Non-Q-wave	197 (26)	169 (22)	141 (30)	129 (27)
Other	12 (2)	32 (4)	13 (3)	13 (3)
Radionuclide ejection fraction				
Mean ejection fraction	0.45 ± 0.14	0.46 ± 0.14	0.47 ± 0.15	0.47 ± 0.14
< 0.20	10 (3)	10 (3)	3 (1)	3 (1)
0.20–0.29	37 (11)	30 (10)	24 (11)	29 (14)
0.30–0.39	67 (20)	51 (16)	35 (16)	27 (13)
≥ 0.40	226 (66)	220 (71)	152 (71)	142 (71)
Ambulatory electrocardiogram				
Mean heart rate (beats/min)	72 ± 12	70 ± 12	73 ± 13	71 ± 12
Any ventricular ectopics	584 (87)	578 (87)	361 (90)	360 (86)
≥ 10 ventricular ectopics beats/hour	101 (15)	108 (16)	83 (21)	69 (17)
≥ 3 ventricular ectopic beats in a row	55 (8)	74 (11)	47 (12)	49 (12)
Medication				
Antiarrhythmic agents	67 (9)	62 (8)	50 (11)	42 (9)
β blockers	390 (51)	393 (52)	268 (57)	287 (61)
Digitalis	99 (13)	95 (13)	74 (16)	76 (16)
Diuretic agents	114 (15)	116 (15)	172 (37)	170 (36)

*New York Heart Association functional classification 1 month before entry.

†Pulmonary congestion by x-ray categorized as mild, moderate or severe.

Values are mean ± standard deviation.

Figures are numbers of patients followed by percentage in parentheses.

significant ($p < 0.0001$, paired sample analysis) in both groups with and without hypertension, whereas no consistently significant reductions were observed in the group taking placebo.

End points: The 1-year placebo- and diltiazem-related cardiac event rates for those with and without a history of hypertension, subdivided by the presence or absence of pulmonary congestion, are listed in Table III. Patients with hypertension had lower 1-year cardiac event rates with diltiazem than with placebo, and this was particularly evident in hypertensive patients without pulmonary congestion during the index infarction. The cumulative rate of first recurrent cardiac events was lower ($p < 0.05$) over the entire follow-up in the diltiazem- than in the placebo-treated patients with hypertension without pulmonary congestion (Figure 1).

A similar beneficial effect with diltiazem was not observed in patients without hypertension. One-year and cumulative cardiac event rates were higher with diltiazem than with placebo in patients with pulmonary congestion in both subgroups with and without hypertension (Table III).

Using the Cox proportional-hazards regression model, the diltiazem:placebo hazard ratios for cardiac events in patients with and without a history of hypertension, subdivided by the presence or absence of pulmonary congestion, are listed in Table IV. The diltiazem:placebo hazard ratio was favorable (hazard ratio considerably less than unity) in patients with hypertension, particularly in those without pulmonary congestion. The diltiazem:placebo hazard ratio was unfavorable (hazard ratio considerably greater than unity) in

TABLE II Blood Pressure and Heart Rate Parameters Before and Two Hours After Initiation of Placebo and Diltiazem Medication in Patients Without and With History of Hypertension

	No Hypertension		Hypertension	
	Placebo (n = 748)	Diltiazem (n = 741)	Placebo (n = 457)	Diltiazem (n = 458)
Systolic BP (mm Hg)				
Before	113 ± 14	112 ± 14	121 ± 16	120 ± 16
After	112 ± 14	109 ± 13	120 ± 17	116 ± 16
p Value*	0.12	<0.0001	0.23	<0.0001
Diastolic BP (mm Hg)				
Before	71 ± 9	70 ± 9	75 ± 10	74 ± 10
After	70 ± 9	68 ± 9	75 ± 10	72 ± 10
p Value*	0.09	<0.0001	0.21	<0.0001
HR (beats/min)				
Before	72 ± 13	72 ± 13	73 ± 15	73 ± 14
After	72 ± 13	70 ± 12	73 ± 14	71 ± 13
p Value*	0.02	<0.0001	0.81	<0.0001
Systolic BP × HR (U)†				
Before	82 ± 19	80 ± 18	88 ± 22	87 ± 20
After	80 ± 18	76 ± 17	88 ± 22	82 ± 18
p Value*	0.003	<0.0001	0.30	<0.0001

*p value by paired t test.

†Units are mm Hg × beats/min/100.

Blood pressure and heart rate values are mean ± standard deviation.

BP = blood pressure; HR = heart rate.

patients with pulmonary congestion regardless of the presence or absence of hypertension. A pattern of bidirectional effects between diltiazem and the absence or presence of pulmonary congestion was evident in both the hypertensive and nonhypertensive patient groups. Hypertensive patients without pulmonary congestion (77% of the hypertension group) had diltiazem:placebo hazard ratios considerably less than unity (hazard ratio = 0.67 and 0.65 for first recurrent cardiac events

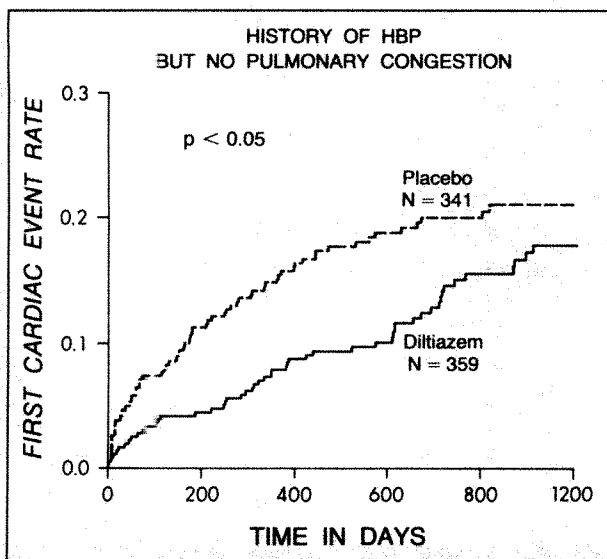


FIGURE 1. Cumulative rate of first recurrent cardiac events (Kaplan-Meier analysis) according to treatment in patients with a history of hypertension but no pulmonary congestion. HBP = high blood pressure.

TABLE III One-Year Cardiac Event Rates in the Placebo- and Diltiazem-Treated Patients Without and With History of Hypertension Subdivided by the Absence and Presence of Pulmonary Congestion

	Event Rate at One Year* (%)			
	First Recurrent Cardiac Event		Cardiac Death	
	Placebo	Diltiazem	Placebo	Diltiazem
No hypertension (n = 1,486)	10.1	11.5	4.9	6.7
No pulmonary congestion (n = 1,208)	9.3	8.1	4.2	3.6
Pulmonary congestion (n = 278)	14.5	25.8	8.5	19.4
Hypertension (n = 911)	17.8	11.6	9.6	7.1
No pulmonary congestion (n = 700)	15.5	7.9	8.0	3.7
Pulmonary congestion (n = 211)	23.3	27.2	14.3	21.0

*From the Kaplan-Meier cumulative-event curves.

TABLE IV Diltiazem:Placebo Hazard Ratios in Patients Without and With History of Hypertension Subdivided by the Absence and Presence of Pulmonary Congestion

	Hazard Ratio* (95% confidence limits)	
	First Recurrent Cardiac Event	Cardiac Death
No hypertension (n = 1,486)	1.06 (0.81, 1.37)	1.29 (0.91, 1.83)
Pulmonary congestion, absent (n = 1,208)	0.86 (0.63, 1.18)	0.93 (0.59, 1.44)
Pulmonary congestion, present (n = 278)	1.63 (0.99, 2.69)	2.29 (1.25, 4.19)
Hypertension (n = 911)	0.77 (0.58, 1.01)	0.87 (0.60, 1.25)
Pulmonary congestion, absent (n = 700)	0.67 (0.47, 0.96)	0.65 (0.39, 1.07)
Pulmonary congestion, present (n = 211)	1.32 (0.83, 2.10)	1.66 (0.96, 2.87)

*Ratio of the risk of the cardiac event among patients receiving diltiazem to that among patients receiving placebo. Hazard ratios <1.0 indicate a relative benefit for the diltiazem-treated patients, whereas hazard ratios >1.0 indicate a relative benefit for the placebo-treated patients.

and cardiac death, respectively), whereas the reverse was true for the minority of hypertensive patients (23% of the hypertension group) with pulmonary congestion (hazard ratio = 1.32 and 1.66). Beta blockers had a negligible effect on the diltiazem-hypertension relation.

DISCUSSION

This retrospective analysis of a randomized, double-blind clinical trial suggests that diltiazem treatment of postinfarction patients with a history of hypertension may reduce first recurrent cardiac events and cardiac death during long-term follow-up. This beneficial effect is especially evident in most patients with hypertension without pulmonary congestion during their index infarction (77%). In the minority of hypertensive patients

who had pulmonary congestion during the acute infarction (23%), diltiazem appeared to exert a detrimental effect. The bidirectional interaction between diltiazem and the presence and absence of pulmonary congestion that was uncovered in the primary analysis,¹ and further substantiated using other parameters of left ventricular dysfunction in a subsequent publication,² is shown here to hold both for patients with and without hypertension.

The mechanism of action of the potentially beneficial effects of diltiazem in postinfarction patients with a history of hypertension is unclear. Diltiazem is an effective antihypertensive agent,^{3,8,9} and reduction of systemic vascular resistance may exert a favorable afterload reduction effect on the left ventricle. Although diltiazem significantly reduced blood pressure, heart rate and the pressure-rate product within 2 hours after the initial 60-mg diltiazem dose (Table II), the magnitude of the reductions were small, averaging about 3% from the control value. We doubt that the beneficial effects of diltiazem in postinfarction patients with a history of hypertension are simply a result of the modest afterload reduction. We hypothesize that in the absence of pulmonary congestion, diltiazem favorably inhibits dysfunctional calcium-mediated ventricular hypertrophy that can develop in the uninfarcted ventricular myocardium.¹⁰ This hypertrophy-inhibiting effect of diltiazem may explain the beneficial result in patients with well preserved ventricular function and the detrimental findings in patients with left ventricular dysfunction. In the latter group of patients, ventricular hypertrophy may be necessary to compensate for extensive myocardial infarction and fibrosis.¹¹ Laboratory and clinical^{12,13} studies have shown that dysfunctional ventricular remodeling begins early after large anterior myocardial infarctions. Diltiazem may exacerbate this process in the vulnerable heart by inhibiting compensatory hypertrophy.

The observed findings with diltiazem were independent of any β -blocker therapy that the patients were receiving. Beta blockers were included in the Cox model, and had a negligible effect on the diltiazem-hypertension results. Furthermore, there was no 3-factor diltiazem-hypertension β -blocker interaction.

There are several limitations to this retrospective subset analysis. The MDPIT was not designed to test the scientific hypothesis that treatment with diltiazem would reduce cardiac events in postinfarction patients

with a history of hypertension, and the present analysis was undertaken after the conclusion of the trial. The current findings, observed after considerable data exploration, must be interpreted with caution. However, there was good balance between treatment groups in baseline variables both for those with and without hypertension. Furthermore, the bidirectional diltiazem-pulmonary congestion effect observed in the current hypertension analysis is similar to that observed in the original report.¹ The diltiazem-related findings in the hypertension and pulmonary congestion analyses are similar for both end points, i.e., for a first recurrent cardiac event and for cardiac death, so there is internal consistency. Thus, the findings suggest that diltiazem may exert a long-term beneficial effect in postinfarction patients with a history of hypertension, especially in most patients who do not develop pulmonary congestion during the acute infarction, and a detrimental effect in the minority who do develop pulmonary congestion.

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Comparison of the Predictive Characteristics of Heart Rate Variability Index and Left Ventricular Ejection Fraction for All-Cause Mortality, Arrhythmic Events and Sudden Death After Acute Myocardial Infarction

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Heart rate (HR) variability index and left ventricular ejection fraction (EF) were compared for the prediction of all-cause mortality, arrhythmic events and sudden death in 385 survivors of acute myocardial infarction. For arrhythmic events, where, for a sensitivity of 75%, HR variability index had a specificity of 76%, EF had a specificity of only 45%. An EF of $\leq 40\%$ had a sensitivity of 42% and a specificity of 75% for arrhythmic events; for the same sensitivity an HR variability index of 20 U had a specificity of 92%. An EF $\leq 40\%$ had a sensitivity of 40% and a specificity of 73% for sudden death; HR variability index had a specificity of 83% for the same sensitivity. For all cause mortality, where, for a sensitivity of 75%, HR variability index had a specificity of 52%, EF had a specificity of 40%. It is concluded that HR variability index appears a better predictor of important postinfarction arrhythmic complications than left ventricular EF, but both indexes perform equally well in predicting all-cause mortality.

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The clinical value of any prognostic variable is determined by how well it predicts and explains specific events. A low left ventricular (LV) ejection fraction (EF) is a consistent predictor of postinfarction morbidity and mortality¹⁻³; but because it does not identify the specific causes of these complications, it makes only an indirect contribution to clinical management. It has recently been shown that depressed heart rate (HR) variability index or baroreflex sensitivity reflects sympathovagal imbalance^{4,5} and is associated with in-hospital mortality,⁶ subsequent all-cause mortality,⁷ arrhythmic events⁸ and sudden death⁹⁻¹¹ after myocardial infarction. Kleiger et al⁷ used the standard deviation of the RR intervals of normal cycles as an index of vagal tone, and found that over a 31-month follow-up period, patients with an RR standard deviation ≤ 50 ms had a mortality of 34%, those with an RR standard deviation ≥ 100 ms had a mortality of 9.0%, and patients with intermediate values had a mortality of 14%. Farrell et al¹⁰ later reported that a low HR variability index had a sensitivity of 85% and a specificity of 74% for predicting arrhythmic events after myocardial infarction. They also found that the combination of a low HR variability index with ventricular late potentials had a sensitivity of 60% and a positive predictive value of 32% for arrhythmic events; characteristics superior to those obtained from the combination of a low EF and frequent ventricular ectopics.

Because LVEF is the standard against which other prognostic variables must be compared, we compared the indexes of HR variability and LVEF for the prediction of all-cause mortality, arrhythmic events and sudden death in 385 survivors of acute myocardial infarction.

METHODS

Patient population: The study population consisted of 477 patients aged <70 years admitted to our hospital with acute myocardial infarction. Acute myocardial infarction was diagnosed if 2 of the following 3 criteria were met: (1) characteristic chest pain lasting ≥ 30

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minutes; (2) a sequential increase and decrease in plasma concentrations of aspartate transaminase, β -hydroxybutyric dehydrogenase or creatine phosphokinase with a peak concentration at least twice the upper limit of normal for our laboratory; and (3) development of new pathologic Q waves or persistent ST/T changes suggestive of non-Q-wave infarction. Only patients admitted straight from home and who survived the acute phase of myocardial infarction were enrolled in the study and studied prospectively. Ninety-two patients were excluded: these included those with important noncardiac disease, a history of previous cardiac surgery or permanent pacemaker insertion, or those who were unable to be followed up. Patients with atrial fibrillation, left bundle branch block and those in whom ambulatory monitoring or assessments of EF could not be performed were also excluded. Of the 477 patients, 385 (80.7%) are reported. These patients were followed up for ≥ 5 months (range 151 to 1,618 days). There were 44 deaths, 14 of which were sudden. Based on the Cardiac Arrhythmia Pilot study,¹² sudden death was defined as death within an hour of the onset of new symptoms, but also included those who died during sleep. There were 26 patients with arrhythmic events, including the 14 sudden deaths; 12 others had symptomatic, sustained (lasting >30 seconds) ventricular tachycardia documented electrocardiographically.

Ambulatory twenty-four-hour electrocardiograms:

Ambulatory twenty-four hour electrocardiograms were recorded at a median of 7 days (range 5 to 10) after infarction using a Reynolds Tracker 2-channel recorder (leads II and CM₅). The sequence of durations of the intervals between adjacent QRS complexes of normal morphology was analyzed by using the Pathfinder III system, Mk 2 (Reynolds Medical Ltd). None of the patients were receiving specific antiarrhythmic therapy but 153 (40%) patients were taking β blockers.

Heart rate variability index: As previously described^{13,14} HR variability index was calculated for each patient. First, the frequency distribution of durations of normal-to-normal RR intervals was constructed. Measured values of HR variability were then obtained in technical units by measuring the baseline width of the distribution curve (Figure 1). Each unit corresponded to $1/128$ s (≈ 7.8 ms). This method of triangular interpolation of the frequency distribution of normal-to-normal interval duration is not affected by low levels of noise and artifact, whereas the widely used methods based on the standard deviation of normal-to-normal interval durations require artifact-clear recognition of the long-term electrocardiogram.¹³

Left ventriculography: Before discharge from the hospital, the patients performed a symptom-limited treadmill exercise test using a Bruce protocol. Patients ($n = 218$) with an abnormal test, i.e., patients with ST

depression, an exercise duration of <3 minutes, an increase in blood pressure of <30 mm Hg, or exercise-induced angina had coronary and LV angiography before discharge. LVEF was calculated from the right anterior oblique view with a Mac angiocomputer package based on the formula of Sandler and Dodge.¹⁵ In patients who did not undergo coronary angiography ($n = 167$), radionuclide angiograms were recorded in the supine position and the EFs calculated by the multiple-gated method performed in the 45 to 60 left anterior or oblique projection.² A comparison in 12 patients showed a good correlation between the 2 techniques ($r = 0.8$).

Statistical analysis: The relation between HR variability and LVEF values assessed in individual patients was tested using correlation coefficients. The major end points for analysis were all-cause mortality, arrhythmic events and sudden death. This analysis was carried out in 2 steps. First, the sensitivity and specificity were computed for different dichotomy limits of HR variability and LVEF for predicting all-cause mortality, sudden death and arrhythmic events. To compare the predictive characteristics of HR variability and LVEF for the chosen end points, receiver-operator curves, which express the dependence of the specificity on the sensitivity, were computed for univariate (HR variability or LVEF) and multivariate (HR variability combined with LVEF) stratification.

RESULTS

LVEF ranged from 10 to 87%, whereas the HR variability index ranged from 4.7 to 114.8 U. Figure 2 shows that HR variability and EF were correlated in

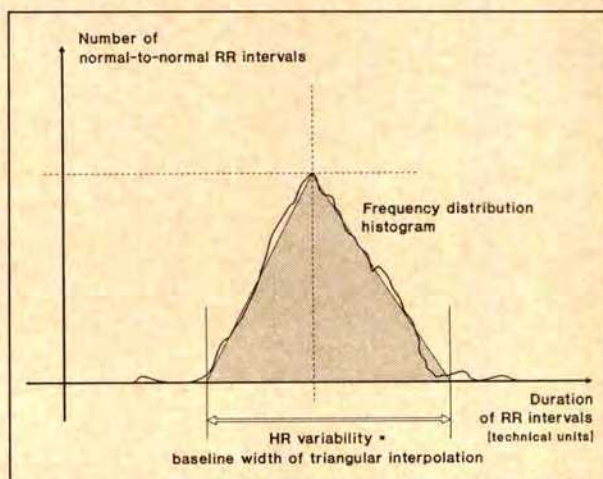


FIGURE 1. For the measurement of heart rate (HR) variability index, the frequency distribution histogram of the normal-to-normal RR intervals was constructed. The curve of the histogram was then approximated by a linear triangular function that had the same maximal point and was the nearest to the frequency histogram (measured by the integral of the square difference). The baseline width of this approximation triangle was taken as the value of HR variability index.

the total population ($p < 0.01$) but that this correlation was weaker in the patients who had arrhythmic events ($p < 0.05$). There was no significant correlation between HR variability and LVEF in the sudden death group.

All-cause mortality: Figures 3 and 4A show the relation between EF, HR variability index and all-cause mortality. Neither EF nor HR variability index usefully predicted all deaths. However, an HR variability ≤ 39 U (baseline width of normal-to-normal duration distribution ≤ 305 ms) had a sensitivity of 75% and a specificity of 52%; for the same sensitivity the EF had a specificity of 40%. An EF $\leq 40\%$ had a sensitivity of 48% and a specificity of 78% for all-cause mortality. The combination of HR variability and the EF appeared to improve specificity for values of sensitivity $< 60\%$ (Figure 4A).

Arrhythmic events: Most arrhythmic events occurred within the first 90 days of infarction. Figure 3 shows that a HR variability index of ≤ 30 U had a sensitivity of 75% and a specificity of 76%; for the same sensitivity, EF had a specificity of only 45%. An EF of $\leq 40\%$ had a sensitivity of 42% and a specificity of 75%. The combination of HR variability index and EF improved specificity for values of sensitivity between 25 and 75% (Figure 4B).

Sudden death: Most (75%) of the sudden deaths occurred within the first 90 days of infarction. Figures 3 and 4C summarize the relation between EF, HR variability index and sudden death. An EF $< 40\%$ had a sensitivity of only 40% and a specificity of 73%. For a sensitivity of 100%, HR variability index had a specific-

ity of 36%, better than for arrhythmic events: for the same sensitivity, EF had a specificity of only 10%. For a sensitivity of 75%, HR variability index had a specificity of 75%, but LVEF had a specificity of only 47%. Specificity increased for values of sensitivity between 25 and 75% when HR variability and LVEF were combined (Figure 4C).

In summary, HR variability index performed better than LVEF, particularly in predicting arrhythmic events and sudden death.

DISCUSSION

A low LVEF is an established predictor of postinfarction complications,¹⁻³ but it does not indicate the specific mechanisms for these events. Autonomic function tests, on the other hand, provide insights into the causes of arrhythmic events after myocardial infarction.^{4,5} We have shown for the first time that, whereas HR variability index and EF do not differ significantly in predicting all-cause mortality, the former is a better predictor of arrhythmic events and sudden death. Thus, we have extended previous findings⁹ by showing that autonomic function tests may provide a more secure basis for postinfarction risk stratification than measurement of the EF.

Differences in the number of patients, the timing of investigations, methods of analysis and the proportion of patients with specific end points make comparisons between studies difficult and may explain some of the discrepancies mentioned later. An EF $\leq 40\%$ in our study had a sensitivity of 48% and a specificity of 78% for all-cause mortality, similar to 50 and 68%, respec-

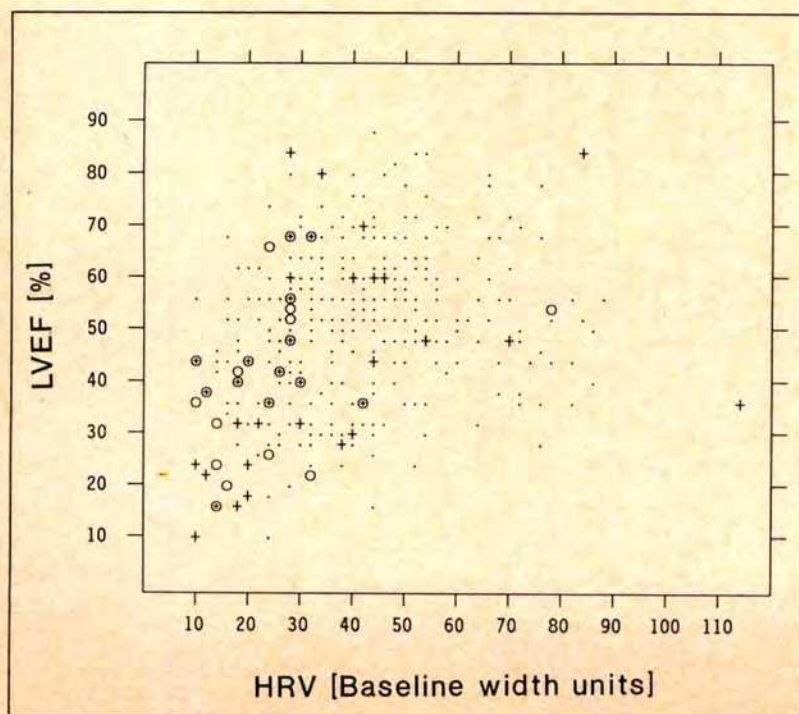


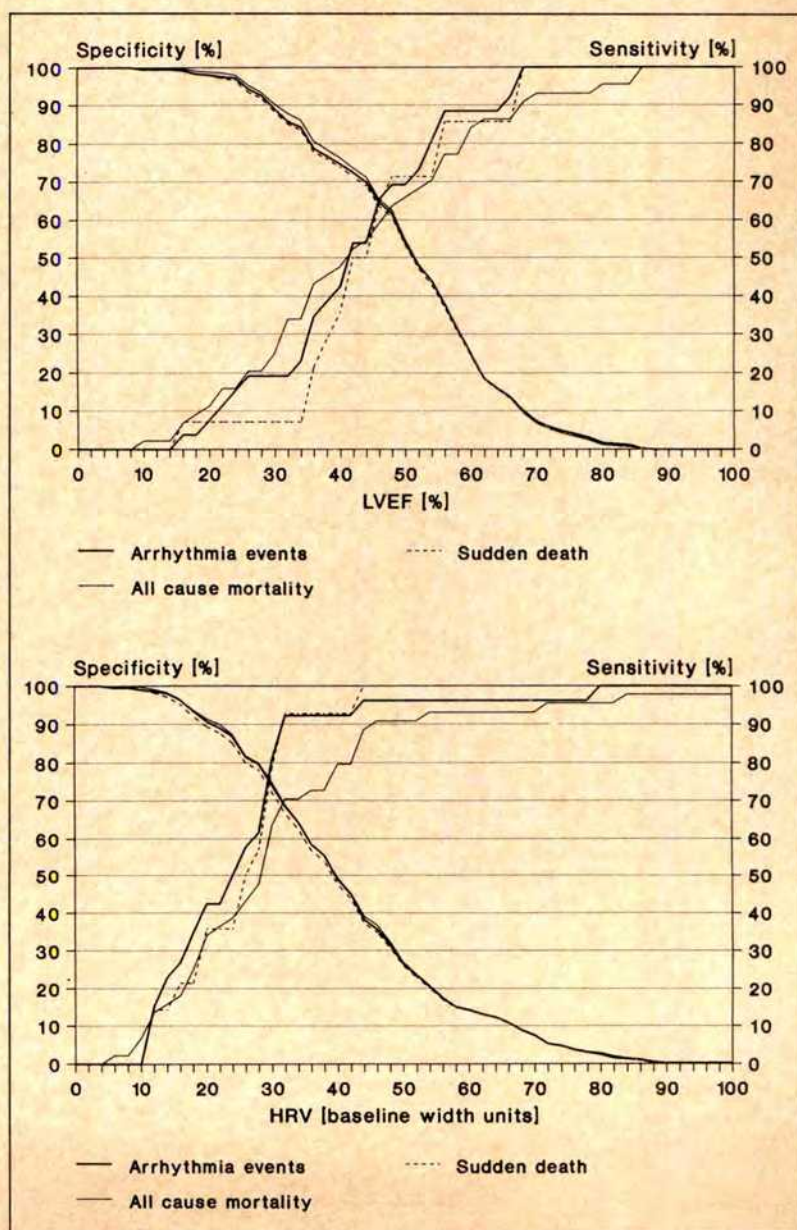
FIGURE 2. A scatter diagram showing the values of heart rate variability (HRV) and left ventricular ejection fraction (LVEF) in individual patients. Crosses in circles, patients who died suddenly; crosses, other patients who died; circles, patients who had ventricular arrhythmias; dots, all other patients. The diagram uses discrete scales with steps of 2% for LVEF and 2 U for HRV index. In cases in which 2 patients have the same values, only 1 mark is printed.

tively, reported by the Multicentre Postinfarction Research Group.³ However, our figures disagree with those of Gomes et al,¹⁶ in whose study of 97 patients, an EF <40% had a sensitivity of 54% and a specificity of 87% for arrhythmic events; the corresponding figures in this study were 42 and 75%, respectively. Our results also disagree with those reported by Schulze et al.¹⁷ In a study of 81 patients, they found that an EF <40% had a sensitivity of 100% and a specificity of 49% for sudden deaths, similar to the results reported earlier by Vismara et al,¹⁸ based on a follow-up of 64 patients. In Schulze's study, the sudden death rate of 14.7% among patients taking antiarrhythmic therapy indicates that a proarrhythmic effect may have contributed to the association between a low EF and sudden death. None of our patients were receiving specific antiarrhythmic therapy when the investigations were performed and an

EF ≤40% had a sensitivity and specificity for sudden death of only 34 and 74%, respectively.

With respect to HR variability, our figures agree with those reported by Kleiger et al.⁷ An RR standard deviation <50 ms in their study had a sensitivity of 33.8% and a specificity of 87.9% for all-cause mortality, and in our study HR variability index ≤19 U (or baseline width units ≤150 ms) had a specificity of 96%. Kleiger et al⁷ also found that patients with an RR standard deviation <50 ms and an EF <30% had a mortality of 49% (sensitivity 15%, specificity 97%), whereas those with an EF >40% and an RR standard deviation >100 ms had a mortality of only 7% (sensitivity 8.9%, specificity 78.7%). In the present study, combining the EF with the HR variability index improved the specificity in predicting all-cause mortality when sensitivity was <60% (Figure 4A); the specificity

FIGURE 3. The receiver-operator characteristics for predicting all-cause mortality, arrhythmic events and sudden death by left ventricular ejection fraction (LVEF) (top) and by heart rate variability (HRV) (bottom).



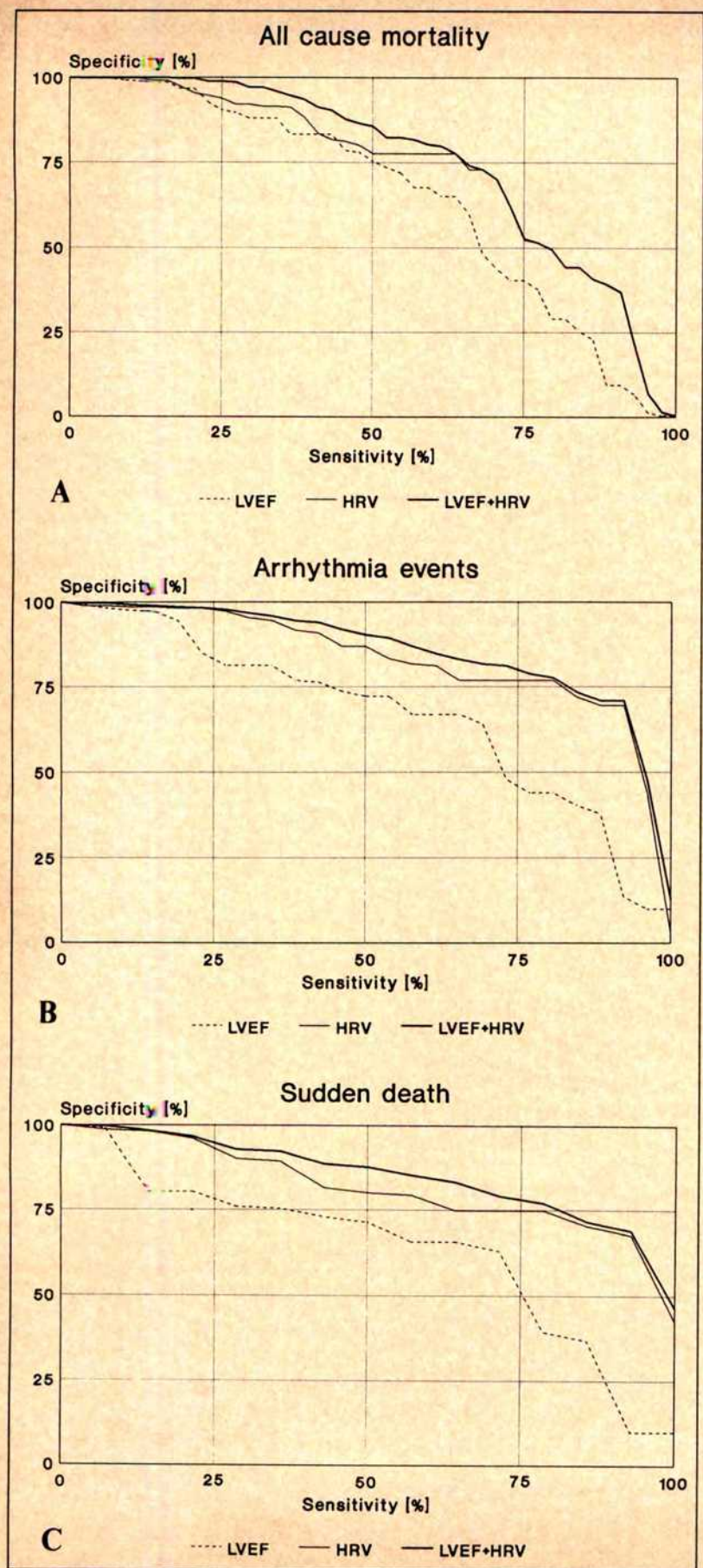


FIGURE 4. The sensitivity and specificity of left ventricular ejection fraction (LVEF), heart rate variability (HRV) index, and their combination, for the prediction of all-cause mortality (A), arrhythmic events (B) and sudden deaths (C).

for arrhythmic events and sudden death for values of sensitivity between 25 and 75% was also improved by this combination (Figure 4, B and C).

Sudden death is usually classified as an arrhythmic event because it is often due to the deterioration of ventricular tachycardia into ventricular fibrillation.^{19,20} The sudden death rate in our study of 4% is similar to those reported by Mukharji et al (5.4%),²¹ Kostis (4.5%)²² and their co-workers, and it constituted 36.4 and 53.3% of all-cause mortality and arrhythmic events, respectively. However, we analyzed sudden death as a separate end point because there is a need to identify those most likely to benefit from expensive or potentially harmful measures such as prolonged antiarrhythmic therapy or the implantation of automatic defibrillators. Furthermore, the predictors of ventricular tachycardia, as such, may differ from those that predict its deterioration into ventricular fibrillation. Finally, a predisposition to ventricular fibrillation itself may not coincide with a propensity to develop ventricular tachycardia. Figures 2 and 4C, e.g., suggest that autonomic dysfunction was uniformly more severe in the subgroup of patients who died suddenly than in the group with arrhythmic events as a whole.

Our results should be interpreted with caution. We used a method for computing HR variability index different from that used in other studies. Also, a depressed HR variability index does not distinguish between particular changes in sympathetic and vagal activity. Such data may be provided by power spectral analysis of Holter electrocardiograms,²³ leading possibly to a rational basis for selecting drug therapy in patients with postinfarction autonomic dysfunction. Another limitation of our study is that LVEF was assessed either by invasive contrast angiography or by radionuclide scans. The predictive characteristics of the LVEF may have also been improved if the true end-systolic and end-diastolic volumes had been calculated and wall motion abnormalities had been considered.

Despite these limitations, it can be concluded that HR variability index is a better predictor of important postinfarction arrhythmic complications than raw LVEF.

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Age-Related Normal Values of Signal-Averaged Electrocardiographic Variables After Acute Myocardial Infarction

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The study examined standard time domain variables of a signal-averaged electrocardiogram (SAECG) in 328 survivors of acute myocardial infarction. The correlation of these variables with age and the influence of age on the prediction of postinfarction arrhythmic complication (sudden death [$n = 12$] or sustained ventricular tachycardia, or both [$n = 14$]) from the SAECG were investigated. Statistically highly significant correlations ($p \leq 0.00002$) between age and SAECG variables were found. Compared with patients aged <60 years, the SAECG-based stratification of arrhythmic complications after myocardial infarction in patients >60 years had lower sensitivity for the same values of specificity and lower specificity for the same values of sensitivity.

It is concluded that (1) the total duration of signal-averaged QRS complexes and duration of the terminal low-amplitude signals increase, whereas the mean voltage of the terminal portion of the averaged complexes decreases with age; (2) in patients surviving myocardial infarction, the criteria for pathologic late potentials should depend on age: the normal values — root-mean-square voltage of the terminal 40 ms of the signal-averaged QRS complex, $\geq 25 \mu\text{V}$; total duration of the signal-averaged QRS complex, ≤ 115 ms; and the duration of low-amplitude signals $<40 \mu\text{V}$, ≤ 37 ms for patients aged <60 years; and root-mean-square voltage of the terminal 40 ms of the signal-averaged QRS complex, $\geq 15 \mu\text{V}$; total duration of the signal-averaged QRS complex, ≤ 125 ms; and the duration of low-am-

plitude signals $<40 \mu\text{V}$, ≤ 43 ms for patients >60 years — have 90% specificity and could therefore be useful thresholds for considering antiarrhythmic intervention; and (3) an abnormal SAECG after acute myocardial infarction is more strongly associated with subsequent arrhythmic complications in younger than in older patients.

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Many reported studies have examined the value of a signal-averaged electrocardiogram (SAECG) for identifying patients who are at high risk of arrhythmic events after myocardial infarction.^{1–9} Most of these studies use 3 standard SAECG variables: root-mean-square voltage of the terminal 40 ms of the signal-averaged QRS complex (RMS-40), the total duration of the signal-averaged QRS complex (tQRS), and the duration of low-amplitude signals $<40 \mu\text{V}$ (LASD-40). The values of these SAECG characteristics that are used to define the presence of pathologic late potentials are reported to be influenced by other clinical variables, such as the infarct site.⁹ This study investigates the influence of age on the values of standard SAECG variables. The aim of the study is to establish whether different criteria for the definition of pathologic late potentials should be applied to different age groups of patients after acute myocardial infarction.

METHODS

Patient population: The study examined 328 patients, aged 31 to 74 years, who were admitted to the hospital with acute myocardial infarction and who survived to discharge. Acute infarction was diagnosed as the presence of 2 of the 3 following criteria: (1) chest pain of ischemic type lasting ≥ 20 minutes; (2) a sequential elevation and decrease in the plasma concentrations of β hydroxybutyric dehydrogenase, aspartate transaminase or creatine kinase with a peak concentration at least twice the upper limit of the reference range

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TABLE 1 Summary of Patient Population

Age Groups (yr)	Number of Patients					Total
	SD	VT	TD	MI History	Other Patients	
30-35	0	0	0	0	4	4
35-40	0	0	1	0	8	9
40-45	0	0	2	3	19	24
45-50	0	0	0	0	33	33
50-55	1	4	2	4	49	58
55-60	6	4	9	7	50	68
60-65	3	3	5	9	50	64
65-70	1	2	9	11	33	51
70-75	1	1	4	5	10	17
Total	12	14	32	39	256	328

MI = myocardial infarct; SD = sudden death; TD = total death; VT = sustained ventricular tachycardia.

of local laboratory; and (3) development of new pathologic Q waves or persistent ST/T changes suggestive of non-Q-wave infarction. Patients were excluded if they had noncardiac disease likely to increase mortality, important nonischemic cardiac disease, a history of previous cardiac surgery or permanent pacemaker insertion, and if they were unable to be followed up. Patients with bundle branch block or ventricular preexcitation were excluded because the wide QRS patterns disturb the time domain SAECD analysis. A history of previous myocardial infarction was present in 39 patients who were included.

Patients were followed up for ≥ 6 months (mean follow up 14), during which 32 patients died, 12 of them suddenly (within 1 hour from the onset of symptoms or during sleep) and 14 patients had spontaneous sustained ventricular tachycardia.

Signal-averaged electrocardiography: In each patient, a high gain SAECD was obtained before hospital discharge (days 5 to 11 after infarction) using a system of Arrhythmia Research Technology (model 1200 EPX). The system utilizes Frank orthogonal leads; the sampling rate of 1 KHz, and low and high pass filters of 250 and 25 Hz were used. In each patient 200 to 500 ventricular complexes were averaged; the achieved noise level was $\leq 0.5 \mu\text{V}$. The 3 above-mentioned standard quantitative SAECD variables (RMS-40, tQRS and LASD-40) were computed in each case. Several patients were treated by β blockers but in all cases, the SAECD was obtained when the patient was taking no other antiarrhythmic therapy.

Statistics and data manipulation: The relationship of age to the values of SAECD variables was assessed by correlation coefficients computed individually for each SAECD variable in (1) the whole patient population, (2) patients who had arrhythmic complications (sudden death or ventricular tachycardia), and (3) patients free of arrhythmic complications.

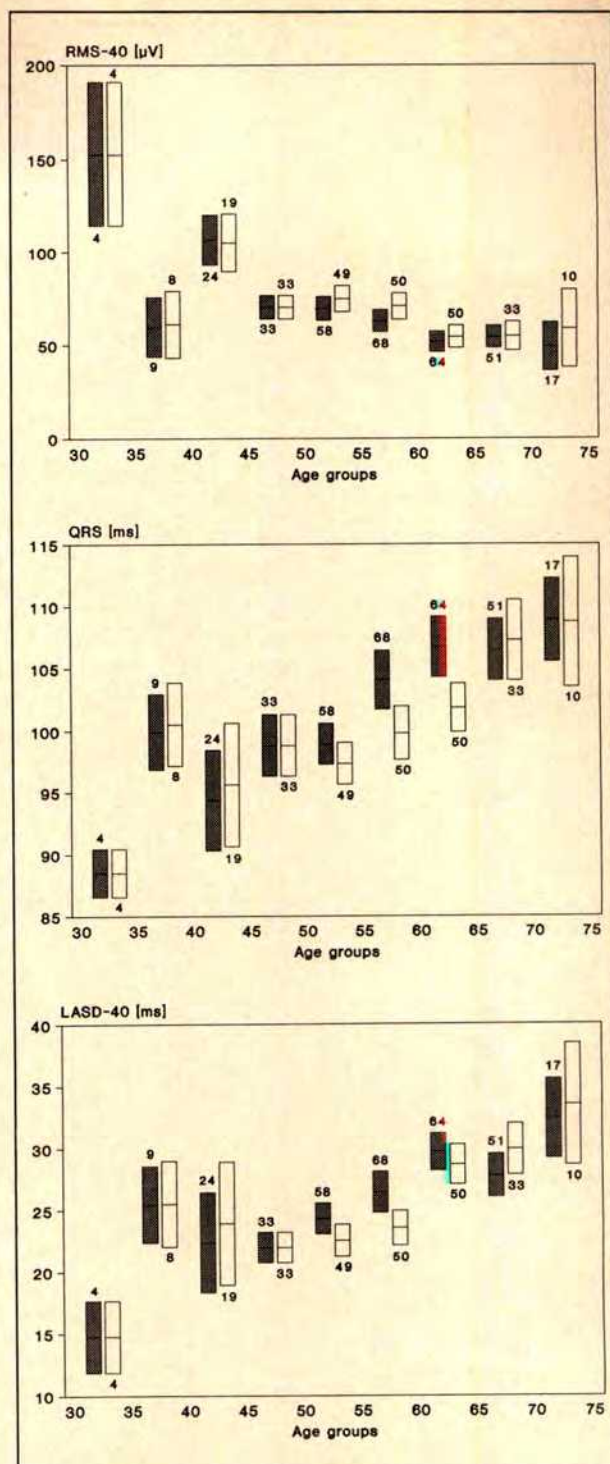


FIGURE 1. Mean values (\pm standard error) of individual signal-averaged electrocardiographic variables in separate age groups. Each part of the figure corresponds to 1 variable (label in the upper left corner, vertical axis). Horizontal axes show separate age groups. For each age group, 2 bars are presented. Shaded bars correspond to the whole populations of individual age groups; open bars correspond to the populations excluding all the end points (arrhythmic events and all-cause mortality) and the patients with a history of infarction. Numbers shown under and above bars indicate numbers of patients in individual groups. LASD-40 = duration of low-amplitude signals $< 40 \mu\text{V}$; RMS-40 = root-mean-square voltage of the terminal 40 ms of the signal-averaged QRS complex.

TABLE II Correlation Coefficients Between Age and Signal-Averaged Electrocardiographic Variables

Patient Group	No. of Pts.	RMS-40	tQRS	LASD-40
Total	328	-0.26745* (0.000005)	+0.24655* (0.00001)	+0.21830* (0.00002)
Arrhythmic event	26	-0.26247* (NS)	+0.04157* (NS)	+0.06800* (NS)
No arrhythmic event	302	-0.25161* (0.00001)	+0.23994* (0.00005)	+0.21110* (0.0001)

*Coefficients.
Numbers in parentheses show the statistical significance of the correlation.
LASD-40 = duration of low-amplitude signals <40 μ V; NS = not significant;
tQRS = total duration of the signal-averaged QRS complex; RMS-40 = root-mean-square voltage of the terminal 40 ms of the signal-averaged QRS complex.

The entire patient population was classified into 9 age groups: from 30 to 35 years, 35 to 40 years, . . . to 70 to 75 years. Mean values of individual SAECG variables were computed for each group. The statistical differences between the values of SAECG variables in those who had arrhythmic complications and in those who remained free of arrhythmic complications were

TABLE III Differences Between Signal-Averaged Electrocardiographic Variables in Patients with Arrhythmic Complications and in Other Patients

Age Groups (yr)	Number of Patients		Statistical Significance		
	SD/VT	Others	RMS-40	tQRS	LASD-40
50-55	5	53	0.1	0.05	0.05
55-60	10	58	0.01	0.00005	0.0001
60-65	6	58	0.05	0.02	0.05
65-70	3	48	NS	NS	NS
70-75	2	15	NS	NS	NS
< 60	15	181	0.002	0.000002	0.000005
≥ 60	11	121	0.05	0.05	0.05

The values of statistical significance (2-sample *t* test) are shown for individual SAECG variables. The columns "SD/VT" and "Others" list the number of patients with and without arrhythmic complications in each age group, respectively.
SAECG = signal-averaged electrocardiographic; other abbreviations as in Tables I and II.

also computed. Standard 2-sample *t* test assuming the same variances of compared samples was used; statistical significance to $p < 0.1$ was considered. The sensitivity and specificity of stratification for arrhythmic complications were computed for each SAECG variable and for all possible dichotomizing values for patients aged $<$ and ≥ 60 years.

RESULTS

Age classification of patient population: The classification of the entire patient population into 9 age subgroups is listed in Table I. Of the total number of arrhythmic complications (26 of 328, 7.9%), the majority occurred in age groups 50 to 55 years (5 of 58, 8.6%), 55 to 60 years (10 of 68, 14.7%) and 60 to 65 years (6 of 64, 9.3%). The remaining 5 events occurred in age groups 65 to 70 years (3 of 51, 5.9%) and 70 to 75 years (2 of 17, 11.8%).

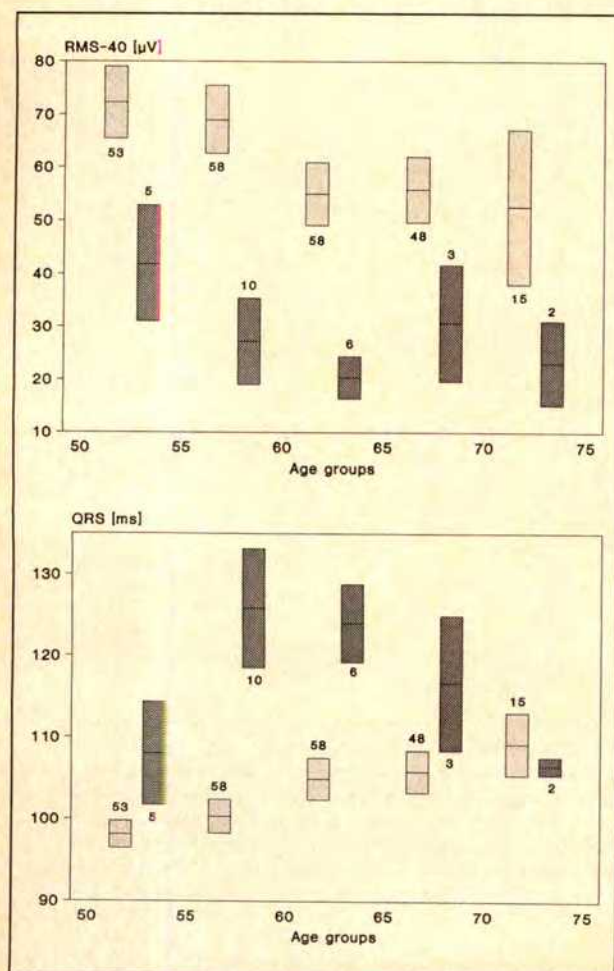


FIGURE 2. Mean values (\pm standard error) of individual signal-averaged electrocardiographic variables in patients with arrhythmic complications and in other patients in separate age groups. Each part of the figure corresponds to 1 variable (label in the upper left corner, vertical axis). Horizontal axes show separate age groups. For each age group, 2 bars are presented. Shaded bars correspond to patients who had arrhythmic complications; stippled bars correspond to the remaining patients in each age group. Numbers shown under and above bars indicate numbers of patients in individual groups. Abbreviations as in Figure 1.

Correlation of signal-averaged electrocardiographic variables with age: Mean values (\pm standard error) of individual SAECG variables in the 9 age subgroups of patients are presented in Figure 1. Apart from the complete subgroups, the figure presents these values for only patients who had a uncomplicated follow-up after a first myocardial infarction (patients with arrhythmic events or death during follow-up and patients with the history of a previous infarction were excluded).

The strong correlation between the mean values of SAECG variables and age that we observed in Figure 1 has been confirmed by computing the correlation coefficients (Table II), but there was no correlation between SAECG variables and age among those with arrhythmic events. In the entire patient population and in those who remained free of arrhythmia complications, the values of age and of each of the SAECG variables were strongly correlated. The value of RMS-40 had negative correlation with age, the values of tQRS and LASD-40 had positive correlation with age.

Age-related stratification of arrhythmic events: No patient aged <50 years had arrhythmic complications during follow-up. Table III lists the statistical differences between the SAECG variables in the patients with arrhythmia and in the remaining patients in age groups 50 to 55 years ... to 70 to 75 years. The table also shows these differences in age groups <60 years. Mean value (\pm standard error) of SAECG variables in individual age groups are shown in Figure 2. The differences between the SAECG variables in patients with and without arrhythmia were statistically significant in groups aged 50 to 55, 55-60 and 60 to 65 years, but were not significant in age groups 65 to 70

and 70 to 75 years; however, the number of patients with arrhythmia in the latter groups was small.

When comparing patients aged <60 and ≥ 60 years, we observed statistically significant differences between patients with and without arrhythmia in both groups, but the levels of significance were much higher in the younger group (see Table III).

The sensitivity and specificity curves of individual SAECG variables for arrhythmic events in groups of patients aged <60 and ≥ 60 years are presented in Figure 3. The dichotomy points for 90% specificity differed for both groups in all variables (RMS-40, $>15 \mu\text{V}$; tQRS, $<126 \text{ ms}$; and LASD-40, $<43 \text{ ms}$ for the group aged ≥ 60 years, and RMS-40, $>25 \mu\text{V}$; tQRS, $<115 \text{ ms}$; and LASD-40, $<37 \text{ ms}$ for the group aged <60 years). In all 3 variables, the sensitivity corresponding to the 90% specificity was higher for the group aged <60 years than for the group aged ≥ 60 years (RMS-40, 60

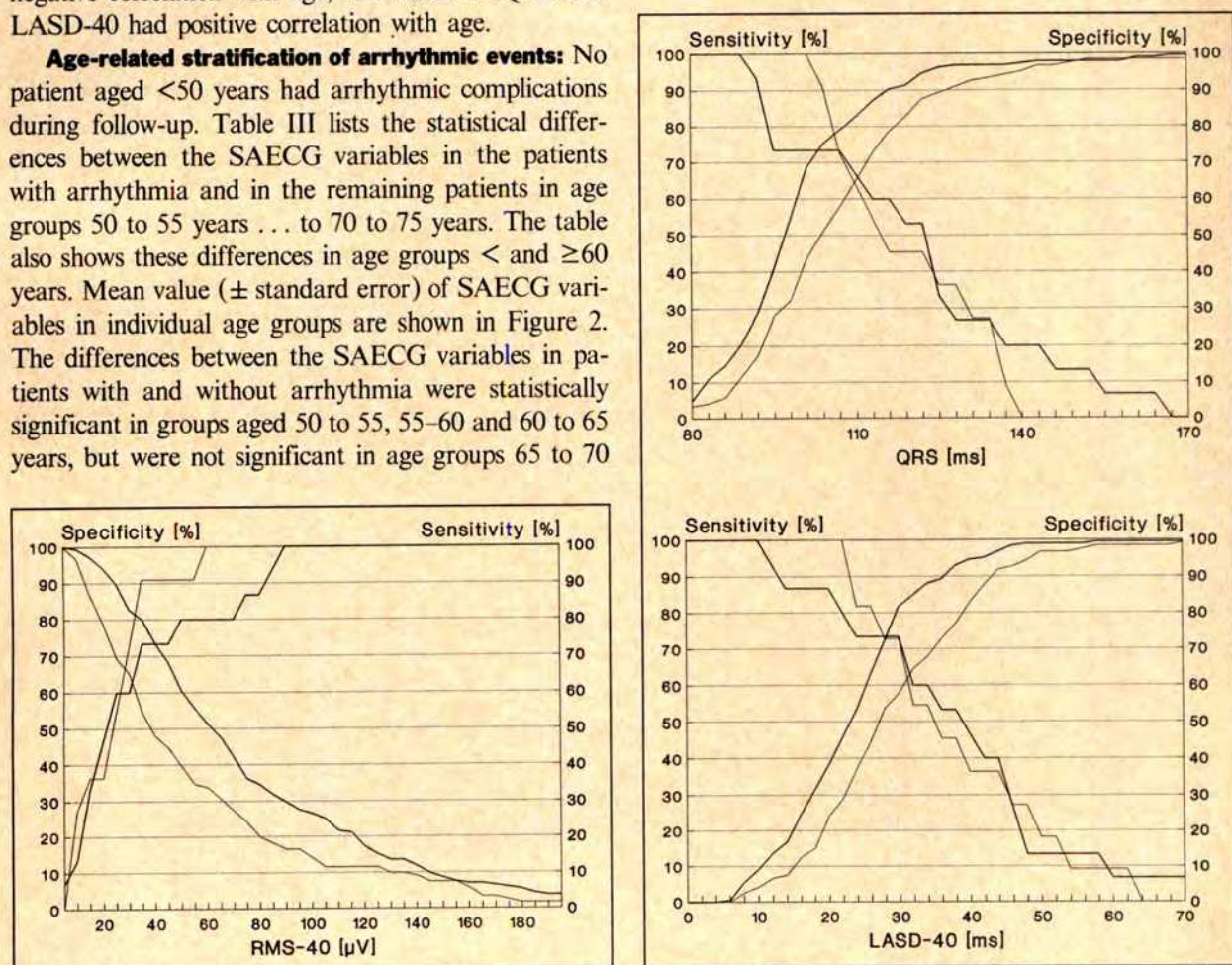


FIGURE 3. Plots of sensitivity and specificity curves of individual signal-averaged electrocardiographic variables used for the stratification of arrhythmic events in the population of patients aged <60 (bold lines) and ≥ 60 (fine lines) years. Each part of the figure corresponds to one signal-averaged electrocardiographic variable (labels at bottom of each part). Horizontal axes correspond to dichotomy points, and vertical axes show values of sensitivity and specificity. Values of sensitivity and specificity are shown for each possible dichotomy point. For example, the selection of a high-risk group based on the criterion LASD-40 $>20 \text{ ms}$ had a specificity of 38% and a sensitivity of 87% for the younger group, and a specificity of 22% and a sensitivity of 100% for the older group. Note that the orientation of the curves in the RMS-40 part is the opposite of that in the tQRS and LASD-40 parts, because low RMS-40 values are pathologic, and low tQRS and LASD-40 values are physiologic. tQRS = total duration of the signal-averaged QRS complex; other abbreviations as in Figure 1.

and 38%; tQ-S, 60 and 38%; and LASD-40, 53 and 38%).

DISCUSSION

Study limitations: The study has been confined to the standard time domain SAECG variables and to the 25- to 250-Hz filter setting. We did not investigate variables of the spectral SAECG analysis, although these might be superior to the time domain variables especially in some selected subpopulations of patients surviving after acute myocardial infarction.

It is not obvious to what extent our observations were influenced by our analysis of the postinfarction population. From the purely physiologic point of view, it might be more appropriate to investigate these age-related phenomena in healthy subjects. On the other hand, the diagnosis of late potentials is one of the very valuable techniques in identifying patients who are at high postinfarction risk. Therefore, the way in which the diagnosis of late potentials is disturbed by the influence of age on the SAECG variables should be addressed in the postmyocardial population.

A history of previous infarction was more frequent in patients aged >60 years and this could have contributed to the observed phenomena. However, when excluding patients with previous infarctions as well as patients with serious postinfarction complications, the correlation between age and SAECG variables was fully preserved (see Figure 1). All recordings were made when the patients were not treated with antiarrhythmic drugs that are likely to influence the SAECG variables; the study did not investigate differences in the use of β blockers between younger and older patients. Other reports have shown that these drugs do not importantly influence the SAECG analysis.¹⁰ On average, younger patients were treated more frequently with β blockers than the older patients. Therefore, the possible effect of β blockers on the SAECG result would have distorted our findings in the opposite direction.

Study implications: Various consistent age-related changes in the normal electrocardiogram have been reported including the alterations in the PR and QT intervals,¹¹ the changes of the electrical axis of ventricular complexes,¹² and QRS durations and amplitudes.¹³ Age-related changes in potential surface maps have also been described.¹⁴ It has been proposed that these changes are due to the degenerative processes within heart tissues, especially within its conduction system.¹¹

A generally slower propagation of excitations wave fronts within the myocardium of patients in the older age groups can easily explain the observed prolongation of signal-averaged QRS durations, as well as the extension of its terminal low-amplitude signals and lower mean voltage of its terminal portion.

The absence of statistical significance between the values of SAECG variables between arrhythmia and uncomplicated cases that we observed in the 2 oldest age groups (65 to 75 years) can be explained by the small numbers of patients who had arrhythmia complications in these groups. Nevertheless, the difference between arrhythmia and uncomplicated cases in patients aged >60 years was more significant in the younger group, and this finding is consistent with the other observation that for the same specificity of identification of arrhythmic events, the individual SAECG variables provide higher sensitivity in the younger patients than they do in the older age groups. These findings suggest that the diagnosis of late potentials is more effective in identifying younger patients who are at postinfarction risk of arrhythmia than in recognising older high-risk patients.

The definition of pathologic late potentials has not yet been standardized and different investigators use different criteria for their diagnosis. However, the strong relation with age was found systematically in all 3 SAECG variables, and it would therefore be surprising if this correlation with age would not affect all of the published clinical criteria for the diagnosis of late potentials.

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Non-Q- and Q-Wave Infarction After Thrombolytic Therapy with Intravenous Streptokinase for Chest Pain and Anterior ST-Segment Elevation

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The clinical features of patients treated with streptokinase for chest pain and anterior ST-segment elevation who subsequently develop non-Q-wave infarction are unknown. Of the 75 consecutive patients who initially presented with chest pain and ST-segment elevation in the anterior leads (V₁-V₆, I, aVL) and were treated with intravenous streptokinase (time from symptoms to treatment averaged <3 hours), 32 (43%) developed a non-Q-wave and 43 (57%) a Q-wave myocardial infarction.

Twenty seven of 32 patients (84%) from the non-Q-wave group and 39 of 43 (91%) from the Q-wave group were studied by angiography at 5.16 ± 2.88 days after the onset of myocardial infarction. Left ventricular end-diastolic pressure was 13 ± 6 vs 20 ± 7 mm Hg ($p < 0.001$), left ventricular ejection fraction was 60 ± 8 vs $49 \pm 14\%$ ($p < 0.001$) and the infarct vessel patency rate was 85 vs 72% ($p = 0.44$) in patients with a non-Q versus a Q-wave infarction, respectively. In summary, when patients presenting with chest pain and ST-segment elevation are treated with streptokinase, a significant portion of these symptoms will evolve into a non-Q-wave infarction. Patients with a non-Q-wave infarction will have a better preserved left ventricular function than patients who develop a Q-wave infarction. This suggests the need for equal distribution of such patients in randomized trials of thrombolytic therapy for acute myocardial infarction to avoid misinterpreting data between groups.

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Classification of myocardial infarction based on electrocardiographic criteria as Q wave and non-Q wave is now well accepted.¹ Within the group with non-Q-wave myocardial infarction, there are 30 to 40% of patients who will present with ST-segment elevation.²⁻⁴ Natural history of patients with myocardial infarction who present only with ST-segment elevation have shown that up to 37% will subsequently develop a non-Q-wave infarction.² Several clinical studies have shown that up to 57% of patients with non-Q-wave myocardial infarction will have a patent infarct artery at angiography even without receiving any thrombolytic therapy.⁵ It is known that intracoronary thrombus plays a pathogenetic role in patients with non-Q-wave myocardial infarction and unstable angina.⁶⁻⁸ Early use of thrombolytic therapy in patients with acute myocardial infarction who present with chest pain and ST-segment elevation is now well accepted. It seems logical to expect, therefore, that widespread use of thrombolytic therapy in patients who present with chest pain and ST-segment elevation will result in a greater number of such episodes that would have evolved into Q-wave myocardial infarctions, to be aborted into a non-Q-wave myocardial infarction.⁹ In addition one would expect that the patency rates of the infarct artery in such patients would also be much higher than in patients with non-Q-wave myocardial infarction who did not receive thrombolytic therapy. There is lack of data in published reports on such patients who are treated with thrombolytic therapy for chest pain and ST-segment elevation that subsequently does not evolve into a Q-wave infarction. The purpose of this study was to analyze this specific subgroup of patients and compare them with patients who subsequently develop Q-wave myocardial infarction.

METHODS

Patients: Seventy-five consecutive patients admitted to our coronary care unit who presented with chest pain and ST-segment elevation in the anterior leads (V₁-V₆, I, aVL) on the electrocardiogram (ECG) and received intravenous streptokinase for suspected acute myocardial infarction were studied. Patients were given strepto-

kinase if they (1) had typical acute chest pain lasting >30 minutes unrelieved by nitroglycerin, (2) had ST-segment elevation >1 mm in 2 contiguous leads, (3) had a total duration of symptoms lasting <6 hours, and (4) were aged <70 years. Patients were excluded if they had (1) previous history of allergy to streptokinase or history of receiving streptokinase in the previous 6 months; (2) history of cerebrovascular accident, major neurologic, thoracic, abdominal or vascular surgery in the past month; (3) cardiac massage during the admission for acute myocardial infarction; (4) severe anemia, bleeding or coagulation abnormality; and (5) incurable primary disease (e.g., cancer) or uncontrolled hypertension (systolic >200 mm Hg, diastolic >110 mm Hg). All patients subsequently had confirmation of the myocardial infarction by an increase and decrease of the creatine kinase-MB isoenzyme.

Treatment regimen: Before starting therapy with streptokinase, all patients received 100 mg of hydrocortisone and 50 mg of pheniramine aminosalicylate intravenously. Lidocaine, 100-mg bolus, was given followed by infusion of 2 mg/min, with adjustment as needed, and was discontinued 24 hours later. Streptokinase, 1.2 to 1.5 million U, was then infused intravenously over 40 minutes. Heparin was initiated after completion of streptokinase infusion, 1,000 U/hour, and was adjusted subsequently by checking the partial thromboplastin time to keep it 1.5 to 2 times the control value. Heparin was usually continued for 5 days after acute myocardial infarction. All patients received routine coronary unit care such as oxygen, analgesics and sedation. Other drugs such as nitrates, β blockers, calcium antagonists and aspirin were used as needed.

Electrocardiographic analysis: All patients had a 12-lead ECG recorded on admission before infusion of streptokinase. Serial ECGs were then recorded daily until discharge from the hospital. Based on serial ECGs, a Q-wave infarction was diagnosed if new Q waves ≥ 30 ms in duration appeared in ≥ 2 contiguous leads. When these were absent, a non-Q-wave infarction was diagnosed. No patient had a Q-wave present on the admission ECG before receiving streptokinase. To quantitate the magnitude of ST-segment elevation, measurement was made 80 ms after the J point with the preceding TP segment as the baseline.

Biochemical investigations: On admission, all patients had serum cholesterol measured. Creatine kinase and its MB isoenzyme were obtained on admission and at 6, 12, and 18 hours after streptokinase infusion and then daily for 2 more days. Time to peak creatine kinase was taken as the time from onset of chest pain to time of peak creatine kinase value.

Catheterization studies: Left-sided cardiac catheterization with coronary angiography was performed in patients at an average of 5.16 ± 2.88 days after the

TABLE I Clinical Characteristics of Patients

	Groups		p Value
	Non-Q-Wave AMI	Q-Wave AMI	
No. of patients	32	43	NS
Age (years)	43 \pm 12	46 \pm 8	NS
Men/women	31/1	40/3	NS
Previous infarction	2 (6%)	2 (5%)	NS
Diabetes mellitus	6 (19%)	9 (21%)	NS
Systemic hypertension	4 (13%)	4 (9%)	NS
Cigarette smoking	19 (59%)	27 (63%)	NS
Family history of CAD	3 (9%)	3 (7%)	NS
Serum cholesterol (mg/dl)	217 \pm 66	221 \pm 48	NS
Dose of SK (million units)	1.33 \pm 0.28	1.42 \pm 0.18	NS
Time to SK (min)	159 \pm 94	167 \pm 105	NS
Concomitant therapy			
Aspirin	17 (53%)	29 (67%)	NS
Nitrates	32 (100%)	43 (100%)	NS
Heparin	32 (100%)	43 (100%)	NS
Calcium antagonists	7 (22%)	5 (22%)	NS
β blockers	1 (3%)	2 (5%)	NS
Peak CK (IU/liter)	1,526 \pm 1,365	3,556 \pm 2,302	<0.001
Time to peak CK (hours)	14 \pm 4	13 \pm 7	NS

AMI = acute myocardial infarction; CAD = coronary artery disease; CK = creatine kinase; NS = not significant; SK = streptokinase; Systemic hypertension = systolic >180, diastolic >90 mm Hg; Time = time from chest pain.

onset of symptoms. Baseline ventricular end-diastolic pressure was measured in all patients. Left ventricular ejection fraction was calculated by the area-length method on all angiograms.¹⁰ A $\geq 50\%$ luminal narrowing of the left main artery, left anterior descending artery, circumflex artery, right coronary artery was considered to represent coronary artery disease. Multiple sites of significant disease in the same coronary artery or its main branches were judged to represent 1-vessel involvement. Significant disease of the left main artery was assumed to be 2-vessel disease. Information from the electrocardiogram during admission, the wall motion abnormalities of the left ventriculogram during angiography and the coronary anatomy was taken to determine which was the infarct-related artery. Patency of the infarct-related artery was determined using Thrombolysis in Myocardial Infarction trial (TIMI) grade classification.¹¹ A patent infarct artery was defined as showing TIMI grade 2 or 3 anterograde flow. An artery showing TIMI grade 0 or 1 was taken to represent an occluded artery. Two experienced angiographers independently interpreted the results of the angiograms.

Statistical analysis: All continuous data are expressed as mean \pm 1 standard deviation. Chi-square and Fisher's exact test were used for discrete proportions and Student's *t* test for continuous data. A *p* value <0.05 was considered statistically significant.

RESULTS

Of a total of 75 patients, 32 (43%) developed a non-Q-wave myocardial infarction and 43 (57%) developed

TABLE II Catheterization Findings

	Groups		p Value
	Non-Q-Wave (n = 32)	Q-Wave (n = 43)	
No. studied	27 (84%)	39 (91%)	
Time (days)	4.38 ± 2.16	5.68 ± 3.21	NS
LVED pressure (mm Hg)	12.85 ± 5.80	19.53 ± 7.10	<0.001
LVEF (%)	60 ± 8	49 ± 14	<0.001
Patency of IRA	85%	74%	NS
Extent of CAD	1.44 ± 1.01	1.72 ± 0.94	NS
No. of coronary arteries narrowed > 50%			
0	5 (19%)	3 (8%)	NS
1	10 (37%)	12 (31%)	NS
2	7 (26%)	14 (36%)	NS
3	5 (19%)	10 (27%)	NS

CAD = coronary artery disease; Extent = number of vessels with > 50% diameter stenosis; IRA = infarct-related artery; LVED = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; NS = not significant; Time = time from admission to catheterization.

a Q-wave infarction. The clinical information of the patients is listed in Table I. There were no differences in age, gender, previous myocardial infarction and major cardiac risk factors between the 2 groups. The dose of streptokinase was also similar and the time from onset of chest pain to streptokinase infusion in both groups was not statistically different and averaged <3 hours. Both groups also received similar concomitant therapy with aspirin nitrates, heparin, calcium antagonists and β blockers. The group with Q-wave infarction had a significantly higher increase in creatine kinase ($p < 0.001$). However, the time from onset of chest pain to peaking of creatine kinase was comparable in the 2 groups.

Angiographic findings (Table II): Twenty-seven of 32 patients in the non-Q-wave group and 39 of 43 patients in the Q-wave group were studied with angiography. The time from admission to angiography in both groups was similar. Patients with non-Q-wave infarction had significantly lower left ventricular end-diastolic pressure (13 ± 5 vs 20 ± 7 mm Hg, $p < 0.001$) and higher left ventricular ejection fraction (60 ± 8 vs $49 \pm 14\%$, $p < 0.001$) than those with a Q-wave infarction. The patency of the infarct-related artery in the non-Q-wave group was higher (85%) than in the Q-wave group (74%), but did not achieve statistical significance ($p = 0.44$). Both groups also showed no difference in the number of vessels affected by significant coronary artery disease or in the distribution of 1-, 2 or 3-vessel disease.

Electrocardiographic data (Table III): When the non-Q-wave and the Q-wave groups were compared, both had comparable ST-segment elevation (5.54 ± 2.3 vs 6.58 ± 3.16 mm, $p = 0.17$). Only 1 in the non-Q-

TABLE III Admission Electrocardiographic Data on Patients

	Groups		p Value
	Non-Q-Wave (n = 32)	Q-Wave (n = 43)	
Maximal ST elevation (mm)	5.54 ± 2.3	6.58 ± 3.16	0.17
Patients with ST elevation			
< 2 mm	1 (3%)	3 (7%)	NS
> 2 mm	31 (97%)	40 (93%)	NS
ST elevation score (mm)	15.65 ± 7.77	21.21 ± 12.36	0.05
No. of leads with ST elevation	4.88 ± 1.58	5.63 ± 1.81	0.10

NS = not significant.

group and 3 in the Q-wave group had ST-segment elevation <2 mm on admission. The Q-wave group had a greater ST elevation score than the non-Q-wave group (15.65 ± 7.77 vs 21.21 ± 12.36 mm, $p = 0.05$).

DISCUSSION

Our study reports the outcome of patients presenting to the hospital with chest pain and ST-segment elevation who were treated with intravenous streptokinase and did not subsequently develop Q-wave myocardial infarction. Since the benefits of thrombolytic therapy in patients with acute myocardial infarction given early after chest pain are now well accepted, all such patients with chest pain and ST-segment elevation will be given a thrombolytic agent if there are no contraindications. There are few studies^{6,8,12-14} dealing with thrombolytic therapy for patients with non-Q-wave infarction and they have reported varying forms of benefits such as opening of an occluded vessel, decrease in the residual stenosis and dissolution of an intracoronary thrombus. A previous study² has shown that in patients who present initially with chest pain and ST-segment elevation, up to 37% will spontaneously develop non-Q-wave infarction and the rest will go on to develop Q-wave myocardial infarction even without receiving any thrombolytic therapy. In the present study, when patients presenting with chest pain and anterior ST-segment elevation were treated with intravenous streptokinase, 43% developed non-Q-wave myocardial infarction. Dewood et al¹⁵ showed that in contrast to a Q-wave infarction, total coronary occlusion of the infarct-related vessel is seen infrequently in the early hours of non-Q-wave myocardial infarction. In their study, 58% of patients with a non-Q-wave myocardial infarction who were studied with angiography between 72 hours and 1 week after symptoms had a patent infarct vessel. This has been suggested to be as a result of spontaneous thrombolysis of a completed thrombotic occlusion of the infarct artery or associated spasm of the vessel superimposed on an atherosclerotic obstruc-

tion. In the present study, patients with a non-Q-wave infarction had a patency of 85% in the infarct vessel on angiography. Thus, it appears that, in addition to the natural spontaneous thrombolysis that is known to occur in such patients, treatment with intravenous streptokinase early after symptoms further increases the patency rate of the infarct artery. When compared with those who did develop a Q-wave, patients with a non-Q-wave infarct had a significantly lower amount of damage to their myocardium as seen by lower creatine kinase levels, lower left ventricular end-diastolic pressure and higher left ventricular ejection fraction. Several studies comparing non-Q and Q-wave infarctions have shown this to be true.^{2,16,17} However, none of these studies used thrombolytic therapy.

Electrocardiographic evolution of acute myocardial infarction after thrombolytic therapy: ST-segment elevation occurs within a few seconds of complete occlusion of a coronary artery. During the next 6 to 8 hours, R waves are lost or their amplitude reduced and pathologic Q waves develop.^{18,19} Many studies have shown that a significant increase in R-wave amplitude and the reduction in the number of pathologic Q waves after reperfusion means salvage of jeopardized myocardium, and use of thrombolytic therapy has supported this concept.²⁰⁻²³ Complete nondevelopment of a Q wave can therefore be taken to indicate much more salvage of an infarcting myocardium. Huey et al² showed that ST-segment elevation of <2 mm on admission is an independent predictor of a subsequent development of a non-Q-wave infarction. In fact, they showed in their study that only 26% of the patients who had >2 mm of ST-segment elevation on admission developed a non-Q-wave infarction. Almost all of the patients in the present study had >2 mm of ST-segment elevation at admission and would be expected to go on to develop Q-wave infarction. However, 44% of these patients developed non-Q-wave infarction, but when compared with the number of patients who developed a Q-wave infarction, this may not achieve statistical significance. In view of what would have been expected by natural history, this supports the fact that early thrombolytic therapy did prevent many of these patients from developing a Q-wave infarction.

Clinical implications: Our data have shown that despite the fact that spontaneous natural thrombolysis would be expected to abort a Q-wave infarction in some patients presenting with ST elevation and chest pain, streptokinase treatment improves the number of such aborted Q-wave infarcts. Additionally, the patency rates of the infarct-related vessel in such patients is much higher after receiving streptokinase than seen in natural history studies, supporting the fact that throm-

bolytic therapy provides an additional benefit to these patients. The results of higher patency rates of the infarct artery and better preserved left ventricular function in non-Q-wave myocardial infarction have been shown in our study only in a very specific subgroup of patients who present with chest pain and ST-segment elevation in the anterior leads on the ECG. Whether these results would also apply to patients who have inferior ST-segment elevation needs further study. Our study supports the caution practiced by Huey et al² to distribute patients with non-Q-wave infarction equally between treatment and control groups in future randomized thrombolytic trials; interpretation of left ventricular function and creatine kinase levels are clearly different in this subset who go on to develop non-Q-wave infarction.

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Effects of Urokinase and Heparin on Minimal Cross-Sectional Area of the Culprit Narrowing in Unstable Angina Pectoris

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The immediate and delayed effects of urokinase and heparin on minimal cross-sectional area of a patent ischemia-producing coronary artery were prospectively investigated in 43 patients with unstable angina. After baseline angiography, patients were randomized to 3 different treatment groups: group I — urokinase (1,000,000 U intravenous bolus dose), followed by heparin infusion 3 hours later; group II — heparin (10,000 U intravenous bolus, followed by continuous infusion); and group III — conventional therapy only (intravenous nitroglycerin, β blockers and calcium antagonists). Angiography was repeated at 1 hour and at 8 days of treatment and minimal cross-sectional area was determined in the 35 patients who completed the study. In group I, minimal cross-sectional area increased from 0.84 ± 0.48 mm² at baseline to 0.94 ± 0.49 mm² at 1 hour ($p < 0.05$), and to 1.00 ± 0.51 mm² at 8 days ($p < 0.01$ vs baseline). In group II, a significant increase in minimal cross-sectional area was observed only at the 8-day angiography (0.64 ± 0.39 mm² at baseline; 0.67 ± 0.37 mm² at 1 hour [$p =$ not significant]; and 0.79 ± 0.48 mm² at 8 days [$p < 0.01$] vs baseline). In group III, no significant changes in minimal cross-sectional area occurred either at 1 hour or at 8 days. Thus, both urokinase and heparin improved lesion geometry in patients with unstable angina, although a large individual variation was noticed. The effect occurred earlier with urokinase than with heparin.

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Heparin and aspirin, as well as thrombolytic agents, have been administered for unstable angina based on the importance of thrombus formation in the development of this syndrome.¹⁻⁷ Although administration of heparin or aspirin, or both, has been found to reduce the rate of progression from unstable angina to myocardial infarction or cardiac death, the efficacy of thrombolytic therapy is still controversial.⁸⁻¹² Results of preliminary investigations with intravenous or intracoronary thrombolytic therapy in unstable angina suggest that this treatment is accompanied by clinical improvement in some patients.¹³⁻²⁰ In a few of these studies, the effect of thrombolytic therapy on the ischemia-producing lesion has been separated from the potential effects of heparin. Additionally, a control population without heparin has not been included for comparison.^{21,22} This investigation separately assesses and compares the effects of either thrombolytic therapy or heparin on cross-sectional area of the ischemia producing coronary lesion in unstable angina. We performed a prospective randomized quantitative angiographic study in patients presenting with acute symptoms of unstable angina and without total coronary occlusion. Data on the immediate and delayed effects of either urokinase or heparin or conventional therapy were compared by quantitative analysis of changes in minimal cross-sectional area of the ischemia-related artery.

METHODS

Study group: The study was performed on 52 consecutive patients (43 men, 9 women, mean age 58 ± 8 years) admitted to the coronary intensive care unit at the Ospedale Maggiore of Novara, Italy, between January 1986 and June 1988, with a diagnosis of unstable angina. Patients were selected according to the following criteria: (1) new onset (< 6 weeks) of recurrent chest pain at rest with accompanying electrocardiographic changes; and (2) recent (< 6 weeks) worsening of ischemic symptoms in patients with previous stable angina or remote myocardial infarction (> 12 months). For admission to the study, documented transient electrocardiographic changes of ST elevation or depression, T-wave inversion or normalization during chest pain were required within 24 hours before angiography. The

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presence of acute myocardial infarction was retrospectively excluded by absence of (1) new Q waves on the electrocardiogram, (2) an increase of creatine kinase-MB isoenzyme activity, or (3) akinetic areas in the involved segments on left ventriculogram.

Shortly after admission to the coronary care unit, patients were treated with intravenous nitroglycerin, 10 to 100 $\mu\text{g}/\text{hour}$, to obtain a stepwise reduction in blood pressure not exceeding 10% of baseline pressure. If the patient still had recurrent chest pain, calcium antagonists (nifedipine 40 to 80 mg/day) and β blockers (to achieve a maximal heart rate not >60 beats/min) were added.

Exclusion criteria: Patients with normal coronary arteries or left main disease, and patients with a contraindication to thrombolytic therapy or anticoagulative treatment were excluded. Patients who had been taking aspirin or anticoagulant drugs in the last 7 days, and those in whom it was either impossible to identify the culprit lesion or the culprit lesion corresponded to a totally occluded vessel, were also excluded.

Definition of the culprit coronary artery lesion: The ischemia-producing lesion was defined according to the criteria of Ambrose et al.²³

Coronary angiography: Coronary arteriography was conventionally performed. Immediately after vascular access, heparin (5,000 U) was given intraarterially. Nitroglycerin infusion (10 to 100 $\mu\text{g}/\text{min}$), initiated in the coronary care unit, was continued during the procedure to obtain maximal coronary vasodilatation and to prevent the occurrence of vasospasm.

Coronary angiograms were obtained in multiple single-plane standard and craniocaudal projections utilizing nonionic contrast medium (iopamidol, Bracco, Italy). For each left anterior oblique projection, a complementary projection was obtained in the right anterior oblique view. The pairs of orthogonal projections best displaying the culprit lesion were selected as baseline angiograms. A biplane left ventriculogram was also obtained in control conditions.

Study protocol: Eligible patients were randomized to 3 treatment groups: group I — urokinase (Serono, Italy) 1,000,000 U intravenous bolus (2 to 4 minutes), and after a time interval of 3 hours followed by heparin infusion for 8 days at a rate of 800 to 1,000 U/hour to maintain a coagulation time 1.5 to 2.0 times higher than control value. Nitroglycerin (10 to 100 $\mu\text{g}/\text{min}$ intravenously) was also administered for 8 days; group II — heparin 10,000 U intravenous bolus followed by an infusion of 800 to 1,000 U/hour for 8 days to maintain a coagulation time 1.5 to 2.0 times higher than control value. Nitroglycerin, 10 to 100 $\mu\text{g}/\text{min}$, was administered intravenously for 8 days; and group III — intravenous nitroglycerin (10 to 100 $\mu\text{g}/\text{min}$) for 8 days.

Coronary angiography was repeated at 1 hour and 8 days during each treatment. Maximal therapy with calcium antagonists and β blockers was also given to all patients and continued for 8 days in the coronary care unit.

The pairs of angiograms recorded at different times (baseline, 1 hour, 8 days) were performed under the same x-ray conditions and equipment setting. A radioopaque marker was filmed to facilitate identification of the pairs of angiograms to be analyzed by an observer, unaware of both treatment and angiographic sequence.

Mean blood pressure was measured and recorded before each angiogram and adjusted by regulation of the nitroglycerin infusion rate in order to maintain similar values for each given patient throughout the study.

Randomization was performed at the time of baseline coronary angiography by opening in sequence consecutively numbered sealed envelopes. A target sample size of 60 patients with 20 assigned to each treatment group could not be achieved due to ethical concerns in continuing the study after the adverse clinical outcome observed in several patients in group III. Administration of study medication was not conducted in a blinded manner. All patients gave their written informed consent to the study.

Qualitative coronary analysis: Coronary lesions were morphologically classified according to Ambrose et al.²³ A consensus of 2 angiographers was necessary for the definition of lesion morphology and identification of thrombi. In case of disagreement, a third angiographer's opinion was decisive.

Quantitative coronary analysis: Quantitative analysis of coronary artery lesions was blindly performed at the University of Iowa, Iowa City, Iowa. The computer-assisted method described by Brown et al was used.²⁴

In the present study, changes in minimal cross-sectional area were chosen to assess the efficacy of treatments. Inter- and intraobserver variability for cross-sectional area measurements in this study were performed on a sample of 50 areas, ranging from 0.11 to 1.72 mm². Intraobserver variability was 5.8% and interobserver variability 6.7%. These figures compare with those obtained in previous studies from the same laboratory.²⁵

Statistical analysis: Data are presented as mean \pm standard deviation. Statistical analysis was performed using a statistical software package. Baseline clinical and angiographic characteristics were compared among the 3 treatment groups using analysis of variance for continuous variables and exact tests for discrete variables. The reduction in minimal cross-sectional area of the ischemia-producing coronary artery was analyzed with the Wilcoxon signed rank-sum test. The choice of a nonparametric approach was based on the not quite

TABLE I Selected Characteristics of Patients (n = 43) at Entry into Study

Characteristics	Group I (n = 12)	Group II (n = 13)	Group III (n = 18)
Age (years)	58 ± 8	55 ± 9	56 ± 10
Male sex (n)	10	10	15
New-onset angina	7	9	10
Worsening angina	3	2	2
Previous myocardial infarction	2	2	4
ST/T transient elevation	7	6	9
ST/T transient depression	5	7	9

normal distribution of minimal cross-sectional area values and the small sample size in each treatment group. Results were considered significant at $p < 0.05$.

RESULTS

Patient characteristics: Of 52 patients considered as potential candidates to the study, 43 were randomized to either urokinase followed by heparin (group I, $n = 12$), heparin alone (group II, $n = 13$), or conventional therapy (group III, $n = 18$). Angiographic criteria were not met in 9 patients who were excluded. Data on age, gender, clinical presentation, presence of a previous myocardial infarction and type of transient electrocardiographic changes during chest pain for the 43 randomized patients are listed in Table I.

Angiographic findings: Table II gives information on the incidence of 1-, 2- and 3-vessel disease, the coronary artery responsible for the unstable angina, minimal cross-sectional area of the involved vessel, lesion morphology and presence of intracoronary thrombus. Twenty-two of 43 patients (51%) had 1-vessel disease; the left anterior descending artery was the culprit coronary vessel in 32 of 43 patients (74%). Lesion morphology was of the concentric type in 14 patients (32%) and of the eccentric type II in 25 patients (58%). Intracoronary thrombus was evident in 10 patients (23%).

Clinical events: After the first catheterization (baseline and 1 hour angiography), 3 patients in group III developed a non-Q-wave myocardial infarction, whereas 5 other patients (1 in group II and 4 in group III) were referred for urgent revascularization because of rapidly progressing clinical deterioration.

Comparability of treatment groups: Comparison of 19 patient characteristics at random assignment among the 43 patients enrolled in the study showed no significant intergroup differences at study entry (Tables I and II). Minimal cross-sectional area of the ischemia-producing lesion at baseline was not significantly different among the 3 treatment groups: group I, 0.84 ± 0.47 mm²; group II, 0.64 ± 0.40 mm²; and group III, 0.68 ± 0.50 mm².

Multivariate analysis with respect to number of diseased vessels, vessel involved, type of lesion and type of electrocardiographic changes did not show intergroup

TABLE II Angiographic Findings of Patients (n = 43) at Entry into Study

	Group I (n = 12)	Group II (n = 13)	Group III (n = 18)
No. of coronary arteries narrowed > 50% in diameter			
1	3	9	10
2	4	2	4
3	5	3	4
Ischemia-producing vessel			
Left anterior descending artery	10	9	13
Circumflex artery	0	3	3
Right coronary artery	2	1	2
Lesion morphology			
Concentric	5	4	5
Eccentric I	0	1	1
Eccentric II	6	7	12
Multiple	1	0	1
Intracoronary thrombus	1	4	2
Mean cross-sectional area (mm ²)	0.84 ± 0.47	0.66 ± 0.40	0.68 ± 0.50

differences. The 8 patients who could not be assessed at the 8-day follow-up because of clinical deterioration were indistinguishable in terms of clinical presentation, coronary angiographic findings and baseline minimal cross-sectional area (0.71 ± 0.36 mm²) from the 35 patients who underwent all phases of the study protocol. No changes in minimal cross-sectional area were observed at 1 hour in these 8 patients (0.69 ± 0.42 mm²), but this occurred also in other patients in group III, who did not experience such worsening of symptoms.

Study group: Thirty-five patients (43 randomized minus 8 patients who were subsequently excluded because of clinical deterioration) completed the study for the comparative evaluation of changes in minimal cross-sectional area over time. They were distributed into the 3 treatment groups as follows: group I (urokinase followed by heparin), 12 patients; group II (heparin alone), 12 patients; and group III (conventional therapy), 11 patients.

Immediate and delayed effects of treatments in these 35 patients are seen in Figure 1. Minimal cross-sectional area increased with time in all 3 study groups. However, a significant improvement from baseline was observed only in groups I and II.

GROUP I: Baseline minimal cross-sectional area of the culprit lesion in this group ranged from 0.16 to 1.73 mm², and averaged 0.84 ± 0.47 mm² (mean ± standard deviation). One hour after administration of 1,000,000 U of urokinase, minimal cross-sectional area increased significantly ($p < 0.05$) to 0.94 ± 0.49 mm² (16% relative to baseline). At 8 days, minimal cross-sectional area increased to 1.00 ± 0.51 mm² (25% from baseline, $p < 0.01$).

Analysis of individual patient response (Figure 1), showed obvious variability in the response to urokinase. Five patients showed a ≥ 0.1 -mm² increase at 1 hour

and 1 of these 5 showed a further increase of ≥ 0.1 mm² at 8 days. One patient had decreased minimal cross-sectional area at 1 hour and no patient had decreased minimal cross-sectional area from 1 hour to 8 days.

Between the 1-hour and 8-day angiography, 6 patients in group I became completely asymptomatic and none of the patients developed acute myocardial infarction.

GROUP II: Baseline minimal cross-sectional area of the culprit lesion in group II varied between 0.16 and 1.79 mm² (mean value 0.64 ± 0.39 mm²; p = not significant vs group I). One hour after the administration of an intravenous bolus of 10,000 U of heparin, minimal cross-sectional area was 0.67 ± 0.37 mm² (6%, p = not significant vs baseline). At 8-day follow-up, minimal cross-sectional area increased to 0.79 ± 0.48 mm² (27% from baseline, $p < 0.01$). Individual patient analysis (Figure 1) again showed obvious variability. One patient had increased minimal cross-sectional area of ≥ 0.1 mm² at 1 hour, whereas 3 patients had increased minimal cross-sectional area ≥ 0.1 mm² at 8 days. Four patients had a slight decrease in minimal cross-sectional area at 1 hour and 1 patient a decreased minimal cross-sectional area at 8 days. One patient in this group did

not undergo the 8-day angiography because of need for urgent revascularization. Of the 12 patients who completed the study, 4 became asymptomatic in the period between 1 hour and 8 days, and 8 patients experienced 1 to 5 episodes of recurrent ischemic chest pain.

GROUP III: For the 11 patients who completed the study, the baseline minimal cross-sectional area of the culprit lesion averaged 0.65 ± 0.48 mm² (p = not significant vs groups I and II). The 1-hour angiography showed a minimal cross-sectional area of 0.69 ± 0.48 mm² (6% increase, p = not significant vs baseline value). At 8-day follow-up, minimal cross-sectional area was 0.71 ± 0.58 mm² (7% increase, p = not significant vs baseline).

Individual patient analysis (Figure 1) showed that 1 patient had increased minimal cross-sectional area ≥ 0.1 mm² at 1 hour, and 2 patients increased minimal cross-sectional area ≥ 0.1 mm² at 8 days. Three patients had a decrease in minimal cross-sectional area at 1 hour, whereas 6 had a decrease in minimal cross-sectional area at 8 days.

Four patients in this group became asymptomatic in the period between the 1-hour and the 8-day study, 5 patients had 1 to 5 episodes of ischemic chest pain and 2 patients had >5 episodes of refractory angina.

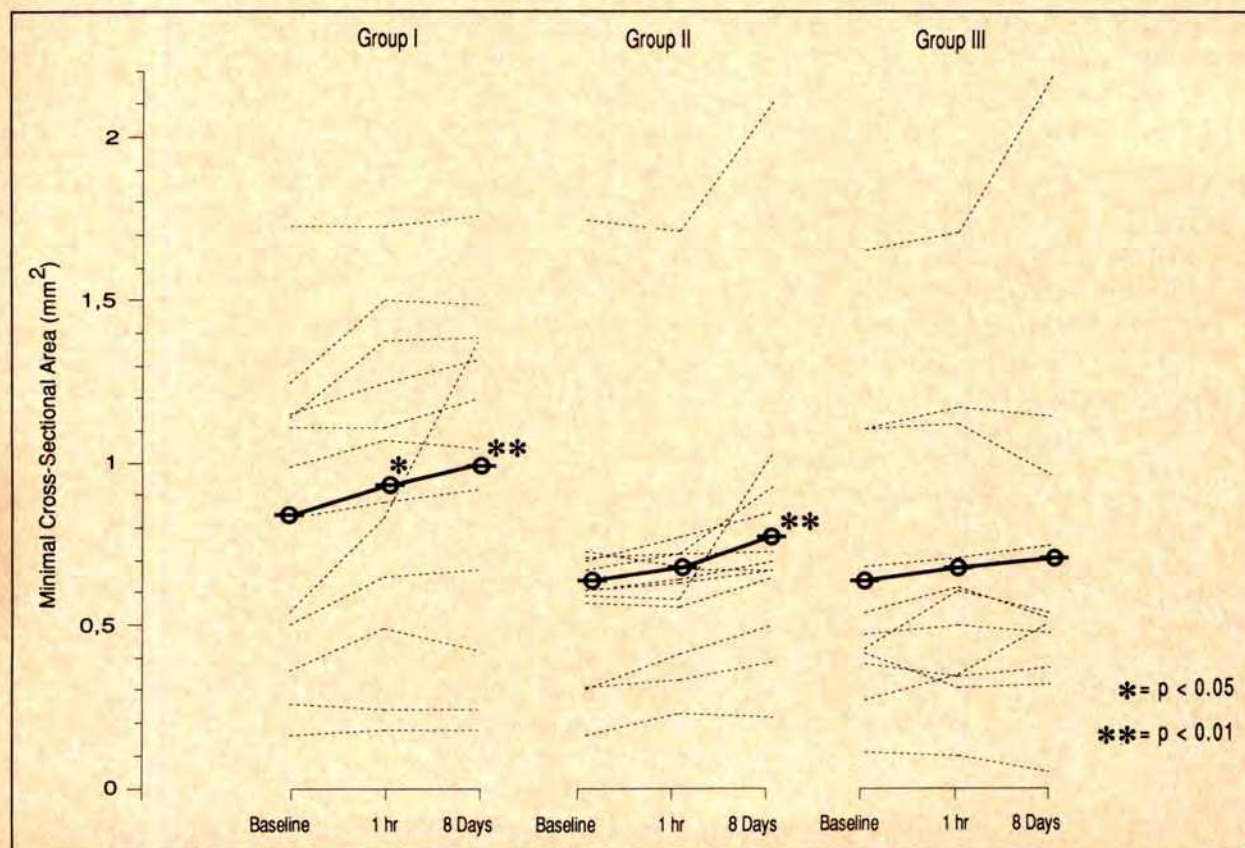


FIGURE 1. Average and individual results of the study (error not represented). In group I, urokinase increased minimal cross-sectional area both at 1 hour and 8 days. In group II, heparin significantly increased minimal cross-sectional area only at 8 days, whereas in group III conventional therapy failed to induce any significant change either at 1 hour or at 8 days.

Qualitative data: Coronary morphologic findings were unchanged at 1 hour in all 43 patients, and at 8 days in the 35 patients who completed the study. A distal filling defect present in 1 patient in group I was lysed at 1 hour; filling defects in patients in groups II and III were still noted at 1 hour and 8 days. Two patients in group II, however, had improvement in coronary flow at 8 days.

Complications: No serious complications or side effects occurred during the study. No hypotension, allergic reaction, serious bleeding or arrhythmias requiring therapy were observed after the intravenous bolus of urokinase was administered.

DISCUSSION

In this prospective randomized study, urokinase administered during the acute phase of unstable angina as a single intravenous bolus produced a statistically significant improvement in minimal cross-sectional area of the ischemia-producing coronary artery lesion, detectable as early as 1 hour after administration. Heparin also significantly improved minimal cross-sectional lumen area of the involved vessel, but this effect was evident only at the angiography performed 8 days after initiation of therapy. However, not all patients showed an angiographic improvement, since some of the patients clearly did not respond to therapy.

The design of this study provided advantageous experimental conditions for the detection of a drug effect. First, the study population was carefully selected. Only patients with new onset (<6 weeks) or worsening angina at rest with transient electrocardiographic changes during pain were included. Second, patients randomized to the 3 treatment regimens were well balanced in all baseline study variables. Third, angiography was performed during the acute phase of unstable angina (within 24 hours from the last episode of chest pain). Fourth, baseline, 1-hour and 8-day angiography were obtained under identical conditions of maximal coronary vasodilatation using intravenous nitroglycerin under arterial pressure monitoring. High quality angiograms were recorded while paying careful attention to film acquisition and processing. Fifth, a 1-hour angiography was scheduled in order to assess the lesion's minimal cross-sectional area at the time of peak effect of the thrombolytic agent.

A limitation of the study was the small sample size, owing to both the difficulty in recruiting of patients with the aforementioned characteristics and some ethical concerns related to the adverse clinical outcome observed in several patients assigned to standard medical therapy.

Our angiographic results corroborate the findings of Williams et al,²¹ who reported that a combination of

recombinant tissue-type plasminogen activator, heparin, aspirin, or heparin and aspirin alone can reduce the severity of coronary stenosis 24 to 48 hours after treatment. However, due to some differences in our study design, our results add additional information on both the immediate and delayed effects of the tested drugs. In the Williams study, a true placebo group without any antiplatelet or anticoagulation therapy was not present. Also repeat angiography after drug treatment was performed between 12 and 48 hours after enrollment and not systemically, as in our study, after 1 hour. This may have blunted the possible differences between the heparin plus aspirin group, (defined as "placebo group" by the investigators), and the groups receiving recombinant tissue-type plasminogen activator. Similarly to the study findings of Williams et al,²² the improvement of minimal cross-sectional area observed in our patients after treatment was mild. However, in patients treated with urokinase, the predominant effect occurred at 1 hour after administration, whereas with heparin most of the effect occurred at 8 days of therapy. This is likely related to the thrombolytic effect of urokinase, with dissolution of a small amount of intracoronary thrombus in group I compared with the antithrombotic effect of heparin coupled with endogenous fibrinolysis in group II.

Thus, our results seems to indicate that thrombolytic therapy works more quickly than heparin alone. However, because the study groups were small, it is impossible to know if inclusion of more patients would have altered these findings. The administration of urokinase in the dose tested led to fewer ischemic events than other types of therapy, but this was not designated as an end point of our study. Large randomized trials are required to reach definite conclusions as to the role of thrombolysis in unstable angina pectoris.

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Twenty-Four-Hour Activity of Felodipine Extended Release in Chronic Stable Angina Pectoris

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To investigate the antiischemic efficacy and duration of action of the dihydropyridine calcium antagonist felodipine, 15 patients with stable exertional angina were enrolled in a double-blind, crossover study comparing 2 doses (5 and 10 mg) of felodipine extended release (ER) and placebo given once daily for 1 week. Bicycle exercise tests were repeated at the end of each treatment period 4 and 24 hours after dosing. Four hours after dosing with both felodipine doses, only 5 patients discontinued the exercise test because of >2 mm of ST-segment depression, whereas 10 continued until exhaustion ($p < 0.01$ vs placebo). Compared with placebo, total exercise time was increased by 19% ($p < 0.001$), with no difference between doses. After 24 hours, exercise duration was prolonged up to physical exhaustion in 6 patients taking felodipine 10 mg ($p < 0.05$ vs both placebo and felodipine 5 mg); moreover, 11 patients taking 10 mg and 5 taking 5 mg increased time to 1 mm of ST depression $\geq 15\%$ compared with exercise time during the placebo test. Mean time to 1 mm of ST depression at 24 hours was increased by 8% with 5 mg and by 18% with 10 mg ($p < 0.001$ vs placebo; $p < 0.01$ between doses). Total exercise time at 24 hours was increased with both doses ($p < 0.001$), with greater efficacy with the 10-mg dose ($p < 0.05$ vs 5 mg). This increased exercise tolerance may be attributed to a reduced afterload and increased myocardial oxygen supply: systolic blood pressure at rest was reduced ($p < 0.005$ vs placebo), and rate-pressure product at 1 mm of ST depression was increased ($p < 0.02$ vs placebo). In conclusion, a once-daily administration of felodipine ER provides antiischemic activity for 24 hours; the 5- and 10-mg doses are equally effective 4 hours after dosing, whereas the 10-mg dose is more efficacious at

24 hours. Because no differences in tolerability were observed, the 10-mg dose should be preferred for the once-daily treatment of chronic stable angina.

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Felodipine is a vasoselective dihydropyridine calcium antagonist that reduces myogenic tone in the resistance vessels of both systemic and coronary circulation.^{1,2} Pharmacodynamic studies in patients with coronary artery disease have shown that felodipine reduces coronary resistance and increases coronary blood flow,³⁻⁵ with no evidence of coronary steal⁵; an additional antiischemic effect may result from the reduction in left ventricular afterload caused by its vasodilating effect on systemic circulation.³⁻⁷ The antiischemic activity of felodipine has been demonstrated by using various provocative tests, such as pacing,^{4,8} exercise⁶ and hyperventilation.⁹ Clinical studies using the plain formulation of felodipine have shown an increased exercise tolerance and reduced electrocardiographic ischemia after both acute¹⁰⁻¹² and repeated^{13,14} administration; the antiischemic efficacy of that formulation was shown to last for 12 hours, allowing twice-daily dosing. Recently, an extended release (ER) formulation of felodipine has been developed, with proved 24-hour activity in patients with essential hypertension,^{15,16} but to date, no data have been published on the effect of this particular formulation in chronic stable angina. The aim of this study was to assess the antianginal and antiischemic efficacy and tolerability of once-daily doses of felodipine ER 5 and 10 mg, compared with placebo, after 1-week administration to patients with stable, exercise-induced angina.

METHODS

Patients: Fifteen patients (10 men and 5 women), aged 53 to 65 years (mean 61 years), with stable angina were enrolled in the study and no patient was withdrawn after randomization. Mean duration of angina was 23 ± 13 months. Six patients were taking antianginal medications before inclusion into the study (β blockers and nitrates [$n = 2$], calcium antagonists and

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nitrates [$n = 2$], β blockers and calcium antagonists [$n = 1$], and calcium antagonists alone [$n = 1$]. Eight patients complained of anginal attacks, whereas angina in the other patients was well controlled by antianginal medications or by a limitation of physical activity. In all patients, angina was rapidly relieved by rest or sublingual nitroglycerin. None of the patients complained of an increase in the number, severity or duration of their anginal attacks during the month preceding the study or during the run-in period. Patients were excluded if they had angina at rest, myocardial infarction occurring ≤ 3 months before enrollment, atrial fibrillation, Lown class III or IV ventricular arrhythmias, atrioventricular or bundle branch block, supine blood pressure $>160/100$ mm Hg, valvular heart disease or heart failure. Women of child-bearing potential and patients with anemia (red cell count $<3,500,000/\text{ml}$), clinically relevant abnormalities of liver or kidney function or any serious concomitant illness were also excluded.

Study design: After being gradually withdrawn from any previous antianginal treatment, patients were given placebo for 1 week. Reproducibility of the exercise test was tested on the fourth and seventh day of this period; the tests were considered reproducible if time to 1 mm of ST-segment depression did not vary $>15\%$ between the 2 tests.¹⁷ Eligible patients were then enrolled in a randomized, double-blind, crossover study comparing felodipine ER 5 mg, felodipine ER 10 mg, and placebo each given once daily for 7 days according to a 3×3 latin-square design. On the seventh day of each study period, patients were admitted to the hospital for 24 hours during which they performed 2 further exercise tests: the first on the seventh day at 12 noon, 4 hours after last drug intake, and the second on the eighth day at 8 A.M., 24 hours after drug administration. At each visit, patients were interrogated about their symptoms and were requested to return their unused study medications in order to check compliance with the therapeutic regimen. During the entire study, no other cardiovascular drugs were allowed. The study was conducted in accordance with the declarations of Helsinki and Tokyo.

Exercise tests: All exercise tests were maximal, symptom-limited, and performed on a bicycle according to the multistage method, starting with a load of 25 W that was increased by 25 W every 2 minutes. Blood pressure (cuff sphygmomanometer) and heart rate (from the electrocardiogram) were measured at rest, at the end of each step of the test, at ischemic threshold (ST = -1 mm), at the end of exercise, and every 2 minutes during recovery. A 12-lead electrocardiogram was recorded on paper at a speed of 25 mm/s at rest, at the end of each exercise step, at peak exercise, and at 2, 5 and 10 minutes during the recovery phase. Three

leads (V_2 , V_5 and aVF) were continuously monitored throughout both the test and the recovery phase. Reasons for stopping the exercise test were the onset of typical anginal pain of moderate severity, ST-segment depression ≥ 0.2 mV (2 mm), physical exhaustion, life-threatening arrhythmias or the failure of systolic blood pressure to increase at 2 consecutive steps. All exercise tests were performed by the same investigator, and the electrocardiograms were read manually.

Diary cards: At each visit, patients were given diary cards on which they had to record any anginal attacks and the number of nitroglycerin tablets consumed.

Statistical analysis: Statistical analysis was performed using the Statistical Analysis System (SAS), version 6.03. Efficacy analysis was performed by means of analysis of variance for a latin-square design, followed by orthogonal comparisons (felodipine 5 mg + felodipine 10 mg vs placebo; felodipine 5 mg vs felodipine 10 mg) when the F test had a p value <0.05 . The reasons for stopping exercise were compared by using the binomial test. The data are presented as mean \pm standard deviation.

RESULTS

Blood pressure and heart rate at rest (Table 1):

Four hours after dosing, both felodipine doses reduced mean systolic blood pressure ($p < 0.002$), while mean diastolic blood pressure remained unchanged. Mean heart rate increased by 7 beats/min with 5 mg and by 11 beats/min with 10 mg of felodipine ER ($p < 0.01$). There was no significant difference between doses for any of the measurements. Twenty-four hours after dosing, no differences were observed between felodipine and placebo.

Exercise tolerance and hemodynamics at ischemic threshold:

Four hours after drug administration, all 15 patients developed ≥ 1 -mm ST depression during the placebo test; however, only 9 patients did so with 5 mg and 5 with 10 mg of felodipine. Therefore, statistical analysis on the variables measured at the ischemic threshold 4 hours after drug administration was not performed. Twenty-four hours after dosing, 13 patients developed ≥ 1 mm of ST depression during all 3 exercise tests; the remaining 2 patients developed 1 mm of ST depression during the placebo and 5-mg tests but not during the 10-mg test (where the time to 1-mm ST change was considered equal to the total exercise time). Felodipine 5 mg prolonged mean time to ischemia by 28 seconds ($+8\%$) and felodipine 10 mg by 68 seconds ($+18\%$) ($p < 0.001$ vs placebo; $p < 0.01$ felodipine 10 vs 5 mg). Rate-pressure product at ischemia was increased by 8% with 5 mg and by 14% with 10 mg of felodipine ($p < 0.02$ vs placebo) due to a significant increase in heart rate ($p < 0.01$ vs placebo), while sys-

TABLE 1 Systolic Blood Pressure and Heart Rate at Rest, Rate-Pressure Product and Exercise Time at 1-mm ST Depression (ischemic threshold) and at End Exercise

TABLE 1 Systolic Blood Pressure and Heart Rate at Rest, Rate-Pressure Product and Exercise Time at 1-mm ST Depression (ischemic threshold) and at End Exercise																					
Pt. No.	Age (yr) & Sex	Time (hrs)	Exercise Test Values																		
			Resting Values Standing Position			At Ischemic Threshold						At End of Exercise									
			SBP (mm Hg)			HR (beats/min)			Exercise Duration (sec)			RPP (beats/min mm Hg × 10 ⁻²)			Exercise Duration (sec)			RPP (beats/min mm Hg × 10 ⁻²)			
			P1	F5	F10	P1	F5	F10	P1	F5	F10	P1	F5	F10	P1	F5	F10				
1	61F	4	175	120	130	76	84	80	300	420	—	—	287	311	—	360	420	420	294	311	320
		24	140	135	145	84	80	80	300	300	—	—	280	247	—	360	360	390	315	293	302
2	62M	4	140	130	115	64	76	88	360	420	—	—	179	253	—	420	480	480	225	304	266
		24	110	165	125	84	88	80	360	300	360	—	209	264	218	420	420	420	253	315	257
3	65M	4	125	105	105	72	90	96	420	—	—	—	—	—	277	480	480	480	296	306	272
		24	120	115	100	72	82	100	420	420	—	—	270	280	—	450	460	480	296	288	280
4	66M	4	140	145	125	85	88	84	300	240	360	—	222	198	228	360	300	420	247	247	254
		24	110	140	140	60	68	64	300	240	360	—	179	181	202	360	300	400	204	187	224
5	63M	4	130	120	130	76	100	108	480	—	—	—	236	—	—	540	600	600	252	330	357
		24	130	120	130	84	98	100	420	540	540	—	266	273	300	480	600	600	300	315	328
6	63F	4	120	140	130	72	60	80	360	420	420	—	189	248	225	420	480	480	209	252	273
		24	110	110	110	64	68	80	360	420	360	—	176	216	216	450	450	420	227	247	247
7	60M	4	150	130	120	72	86	88	360	600	—	—	262	294	—	390	600	510	286	294	300
		24	135	150	130	72	80	92	420	480	480	—	148	276	270	450	510	510	153	286	294
8	53M	4	155	125	110	80	76	86	420	540	—	—	300	374	—	480	540	540	336	374	323
		24	140	135	125	68	78	72	420	420	480	—	300	307	263	440	480	540	310	322	313
9	55M	4	150	126	125	76	72	68	300	420	420	—	172	181	139	380	480	480	184	201	160
		24	130	130	120	76	76	64	300	300	420	—	147	150	123	330	360	380	157	166	116
10	60M	4	120	120	110	60	76	64	300	—	420	—	176	—	218	330	600	510	190	266	270
		24	140	105	110	68	56	64	300	360	360	—	144	159	176	360	405	420	158	180	198
11	65M	4	140	125	135	68	68	82	360	—	—	—	180	—	—	420	480	450	200	187	234
		24	130	140	130	64	68	72	360	360	390	—	180	190	228	390	420	390	200	220	228
12	59M	4	115	135	100	76	96	88	420	600	—	—	190	266	—	510	600	660	216	266	270
		24	120	95	110	92	76	88	420	480	600	—	207	201	234	480	540	600	228	225	234
13	58M	4	110	100	100	76	72	96	540	—	—	—	223	—	—	600	660	720	238	232	313
		24	100	100	115	72	76	84	540	540	660	—	195	198	294	600	600	660	209	211	296
14	57M	4	140	110	120	88	84	72	300	480	420	—	204	238	281	360	510	480	219	254	296
		24	140	130	130	80	80	72	300	420	360	—	204	221	194	360	480	420	219	234	208
15	53F	4	140	150	145	78	108	112	360	—	—	—	261	—	—	420	480	420	270	323	297
		24	150	130	140	80	96	92	360	360	420	—	252	255	288	390	420	420	285	304	290
Mean ± SD		4	137(18)	125(14)	120(13)	75(7)	82(13)	86(13)	315(30)	390(104)	405(39)	—	197(22)	216(32)	218(59)	431(76)	514(90)	510(88)	244(45)	277(50)	280(46)
		24	127(15)	127(19)	124(13)	75(9)	78(11)	80(12)	368(75)	369(90)	436(101)	—	211(51)	228(48)	240(52)	421(69)	454(85)	470(91)	234(57)	253(54)	254(55)
F5 = felodipine 5 mg; F10 = felodipine 10 mg; HR = heart rate; P1 = placebo; RPP = rate × pressure product; SBP = systolic blood pressure; SD = standard deviation.																					

TABLE II Reasons for Stopping Exercise Test 4 and 24 Hours After Drug Intake

Reason for Stopping Exercise Test	Placebo		Felodipine ER 5 mg		Felodipine ER 10 mg	
	4th Hour	24th Hour	4th Hour*	24th Hour	4th Hour*	24th Hour†,‡
ST-segment depression ≥ 2 mm (no. of pts.)	12	13	5	15	5	8
Chest pain + ST-segment depression ≥ 2 mm (no. of pts.)	3	2	—	—	—	1
Physical exhaustion (no. of pts.)	—	—	10	—	10	6

*p < 0.01 vs placebo; †p < 0.05; ‡p < 0.05 vs felodipine 5 mg extended release.
ER = extended release.

tolic blood pressure remained unchanged. Individual changes in time to 1 mm of ST-segment depression 24 hours after dosing are shown in Figure 1, where it can be observed that during treatment with felodipine 10 mg, 11 of 15 patients had an increase in ischemic threshold $\geq 15\%$ of the predefined limit of spontaneous variability. With felodipine 5 mg, 5 patients also increased time to 1 mm-ST depression $\geq 15\%$ (and another 2 patients had an increase of 14%), whereas in 2 patients time to ischemia was significantly less than that recorded while taking placebo. Moreover, in 13 patients, a dose-response relation was observed, 10 mg being more effective than 5 mg.

Exercise tolerance and hemodynamics at maximal exercise: Four hours after dosing, both felodipine doses were equally effective in increasing mean total exercise time by approximately 80 seconds (+19%, $p < 0.001$ vs placebo) and rate-pressure product by 14% ($p < 0.002$). Twenty-four hours after dosing, both doses of felodi-

pine were more effective than placebo in increasing exercise time ($p < 0.001$). However, the 10-mg dose was more effective than the 5-mg dose ($p < 0.05$), prolonging exercise time by 12% (vs 8%). Rate-pressure product did not change significantly.

Reasons for stopping exercise (Table II): At the end of the placebo period, the exercise test was discontinued for all 15 patients because of ST-segment depression ≥ 2 mm. Four hours after the administration of both doses of felodipine, only 5 patients discontinued exercise because of electrocardiographic signs of ischemia, while the remaining 10 patients continued up to physical exhaustion ($p < 0.01$ vs placebo). After 24 hours, only the 10-mg dose could prolong exercise duration up to physical exhaustion in 6 patients ($p < 0.05$ both vs placebo and vs felodipine 5 mg).

Anginal attacks and nitroglycerin consumption: Only 2 patients reported anginal attacks during the study: 1 patient had 4 anginal attacks while taking pla-

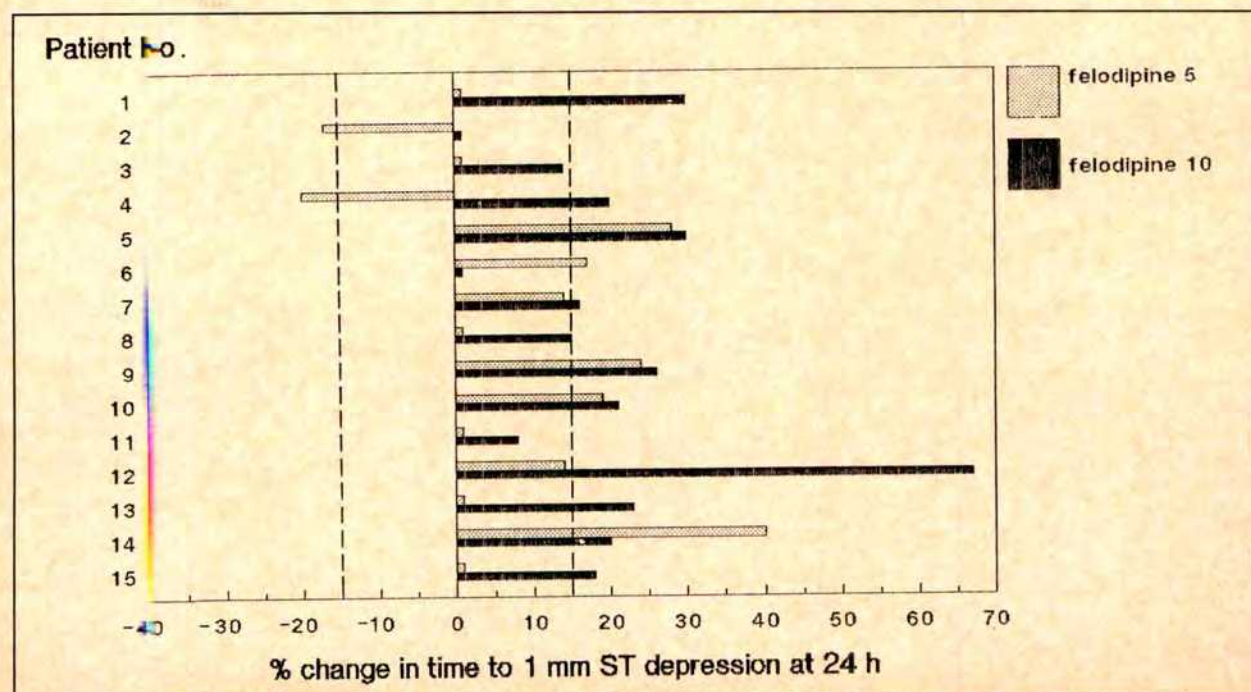


FIGURE 1. Percent change from placebo in time to 1 mm of ST depression 24 hours after the administration of felodipine extended release. Each pair of horizontal bars represents a single patient. The zero axis represents each patient's time to 1 mm of ST depression during the placebo period. The 2 dotted vertical lines corresponding to +15% and -15% represent the limit of predefined casual variability.

cebo and consumed 2 nitroglycerin tablets; 1 had an anginal attack while taking felodipine 5 mg, and consumed 1 nitroglycerin tablet. In both cases, the attacks were of mild to moderate severity.

Tolerability: All patients completed the study without reporting severe adverse effects. Only 1 patient, while receiving treatment with felodipine 10 mg, reported headache of moderate severity that lasted for 3 days and subsided spontaneously without requiring treatment discontinuation.

DISCUSSION

The principal result of this study in patients with chronic stable angina is that the once-daily administration of felodipine ER provides antiischemic activity for 24 hours. In fact, 24 hours after dosing, both time to 1 mm of ST depression and total exercise time were significantly increased by felodipine compared with placebo; moreover, 11 of 15 patients had an increase in time to 1 mm of ST-segment depression equal to or more than the limit of casual variability.¹⁷

Comparison of the effects of felodipine and placebo on time to angina was not possible, since only a small amount of patients developed angina during the exercise test; this may have been due to the rather conservative criterion adopted in our center of stopping exercise at 2-mm ST-segment depression, when many patients still don't complain of chest pain. However, of the 3 patients stopping the exercise test for angina and ST-segment depression during placebo, only 1 reported angina 24 hours after taking felodipine 10 mg. A previous study using 3-mm ST depression as an exercise interruption criterion, and a different exercise protocol, showed a significant prolongation of time to angina lasting for ≥ 10 hours after a single administration of both 5 and 10 mg of plain felodipine.¹¹ In our study, the 5- and 10-mg doses showed a similar efficacy 4 hours after administration, whereas the higher dose was more effective after 24 hours. Individual data also showed a dose-dependent increase in time to 1 mm of ST-segment depression 24 hours after felodipine. This dose-dependence of the duration of the antiischemic effect of felodipine has been previously shown in studies comparing the 5- and 10-mg dosages of the plain formulation,^{11,12} which had similar efficacy at the time of presumed peak drug plasma concentration but where the higher dose was more effective at the trough. Studies in hypertensive patients have shown a clear dose-plasma concentration-effect relation of felodipine in reducing blood pressure,¹⁸ and a longer duration of action of the ER versus the plain formulation of felodipine.¹⁵ On the basis of our data, it may be speculated that the antiischemic effect of felodipine reaches a plateau with the peak plasma concentrations allowed by the 5-mg dosage, whereas the maintenance of a comparable ther-

apeutic effect for up to 24 hours requires the administration of 10 mg once daily. This dosing schedule also seems to be justified by the fact that, as in larger data bases,¹⁸ no differences in tolerability between the 5- and 10-mg doses of felodipine ER were observed by us. However, because all of the effects of both doses of felodipine ER were more marked at 4 than at 24 hours, some patients might take greater advantage from a twice-daily dosing.

The mechanism of felodipine's antiischemic effect has been attributed to a reduction in coronary as well as in systemic vascular resistance,⁴⁻⁷ whereas a reduction in cardiac inotropic state and preload have been excluded.^{19,20} Our data support this hypothesis, since both doses of felodipine reduced blood pressure at rest and increased rate-pressure product at the ischemic threshold and at maximal exercise. This information is in agreement with previous studies with the plain formulation of felodipine,¹² as well as with other dihydropyridine calcium antagonists.^{21,22} In normotensive subjects, the main mechanism responsible for the increased exercise tolerance induced by felodipine appears to be an increased myocardial oxygen supply due to the inhibition of coronary vasomotor tone^{9,23} at the site of the stenosis or in the collateral circulation.² This hypothesis is further supported by our observation of an increased rate-pressure product at the ischemic threshold 24 hours after dosing, while resting blood pressure was no longer different from that when the patients were taking placebo. In addition, Ardissino et al²³ showed greater efficacy of felodipine and nifedipine in patients with exercise-induced angina and a positive response to provocative tests of coronary spasm than in those with a negative response. Finally, the present study was conducted in patients with fixed-threshold angina, a subgroup of the entire population of patients with angina in which coronary vasomotion is considered to play a less important pathogenetic role than in patients with variable threshold or angina at rest.²⁴ The observation of the clinical efficacy of felodipine in this subgroup of patients may also have implications for the investigation of the pathogenetic mechanism of effort angina.

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Ridogrel in the Setting of Percutaneous Transluminal Coronary Angioplasty

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The safety of the combination of heparin and ridogrel therapy and its antiplatelet efficacy was examined in the setting of percutaneous transluminal coronary angioplasty (PTCA). In 32 patients without known aspirin intake for 10 days before PTCA, therapy with ridogrel (300-mg intravenous bolus) was begun just before PTCA and continued orally at a dose of 300 mg twice daily until discharge. Heparin was administered as a 10,000 IU bolus dose before PTCA and followed by an intravenous infusion at a rate of 1,000 IU/hour for 24 hours. Bleeding problems at the arterial entry site occurred in 13 patients, which required a blood transfusion in only 2 patients. One patient underwent emergency bypass surgery without specific problems of hemostasis. Ridogrel virtually eliminated thromboxane B₂ from the serum ($29,990 \pm 6,555$ pg/0.1 ml before vs 63 ± 7 pg/0.1 ml at 2 hours after ridogrel), with a concomitant increase in serum 6-keto-prostaglandin F_{1 α} (511 ± 34 pg/0.1 ml before vs $1,190 \pm 146$ pg/0.1 ml at 24 hours after ridogrel). There were no acute reocclusions in the ridogrel-treated patients, whereas acute reocclusions occurred in 5.6% of the patients taking the standard aspirin + heparin regimen during the same period. Furthermore, at 6-month clinical follow-up patients treated with ridogrel compared favorably with those receiving standard treatment.

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Early acute reocclusion, observed in 2 to 11% of patients the first 24 hours after an initially successful percutaneous transluminal coronary angioplasty (PTCA), remains a major problem.¹⁻⁴ The triggering mechanism is incompletely understood and probably variable.⁵⁻⁸ Endothelial denudation, together with platelet activation and adhesion, is a major stimulant to thrombus formation⁹ and the development of local spasm.^{10,11} Because actual antiplatelet therapy obviously offers no complete solution to the problem, a more potent and selective approach in antiplatelet strategy could be beneficial. Therefore, ridogrel (R68060), a combined thromboxane B₂ synthetase inhibitor and thromboxane-prostaglandin endoperoxide receptor blocker, was compared with salicylate therapy in an open-pilot study in patients undergoing PTCA. The aim was threefold: assessment of the safety of ridogrel in combination with heparin, monitoring of prostanoids and ridogrel concentrations, and collecting observational data on the effect of ridogrel on acute and chronic restenosis rate.

METHODS

Patients: Of 352 patients referred for PTCA at our institution between March 20, 1989, and July 24, 1989, 32 were included in this study. Patients were eligible if they reported no intake of antiplatelet drugs for ≥ 10 days before the study and if no contraindications for this therapy were present. Patients gave informed consent and the study protocol was approved by the ethical committee of our institution.

Study methods: PTCA was performed from the brachial (n = 17) or femoral (n = 15) approach using a standard technique.¹² Ridogrel treatment was administered as a slow intravenous injection of 300 mg just before the start of the PTCA procedure. Twelve hours later, oral treatment was begun at a dose of 300 mg twice daily until hospital discharge. Heparin was given at the start of the procedure as a 10,000-IU intraarterial bolus dose followed by an intravenous infusion for 24 hours at a rate of 1,000 IU/hour with otherwise unchanged concomitant medication. At discharge, ridogrel was replaced by aspirin and a calcium antagonist.

Bleeding events were coded as minor if external and no transfusion therapy was needed. All bleeding episodes requiring blood transfusion were coded as a major

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bleeding complication. Primary PTCA success was defined as a residual stenosis of <50% after PTCA in all treated lesions, without major complications (myocardial infarction, surgery or death). Early acute coronary reocclusion was prospectively defined as the angiographic finding — during the PTCA procedure — of

thrombus formation necessitating reintroduction of the balloon catheter and clinical or electrocardiographic evidence of acute ischemia, or both, occurring at any time before hospital discharge. Lesions were classified according to the recently modified American Heart Association classification.¹³ Late clinical follow-up data consisted of a routine clinical examination 6 months after PTCA, including a maximal bicycle stress test. Patients were specifically questioned for their anginal status and interim events (repeat PTCA, bypass surgery).

Blood samples for plasma levels of ridogrel, serum thromboxane B₂ and 6-keto-prostaglandin F_{1α} were obtained before, and at 2, 4, 8, 12 and 24 hours after the intravenous administration of ridogrel, and then daily just before the next oral drug intake. Plasma levels of ridogrel were determined using a high-performance liquid chromatography method and serum prostanoids by radioimmunoassay.¹⁴ All values were expressed as mean ± standard deviation.

RESULTS

Patients: PTCA was eventually deferred in 1 patient because no significant lesion could be identified during control coronary angiography. In another patient, the PTCA procedure was complicated by an extensive coronary dissection treated by successful emergency bypass surgery (Table 1).

PTCA was a primary success in the remaining 30 patients and none of them had early acute reocclusion.

Bleeding complications: In most patients, ridogrel was well tolerated. Minor bleeding complications were noted in 11 patients (34%). In 5 patients, prolonged bleeding at the brachial arteriotomy entry site occurred, which was managed by manual compression and, in 2 patients, by reduction of the heparin dosage. One of them had an inadvertent tongue bite during PTCA with a local hematoma, resolving over the next 3 days. In 5 patients, a hematoma developed at the femoral entry site, all resolving spontaneously. One patient had a hematoma on his left thigh after a brachial procedure. Major bleeding complications requiring blood transfusion were present in 2 patients (6%). One of them needed a surgical revision for an arterial complication at the site of the brachial arteriotomy and received 2 U of packed red cells. The other developed a large inguinal hematoma after a femoral procedure; 2 U of packed red cells were transfused and the hematoma resolved spontaneously. In the patient undergoing emergency coronary bypass surgery, the increased bleeding tendency was successfully managed by the administration of 5 U of packed red cells and 6 U of fresh frozen plasma, quite similar to the normal amount administered during a routine procedure. Adverse experiences, other than bleeding events, included local pain during intravenous ridogrel injection (n = 4) and a ten-

TABLE 1 Patient and Lesion Characteristics

Age (yr) & Sex	Coronary Artery Narrowed*	Coronary Artery Dilated	ACC/AHA Score	Indication for PTCA
Patients Without Bleeding Complications				
49M	Right	LC	B1	U
58M	Right	LC	C	
61F	LAD	LAD	B2	U
63M	LC	LC	B1	S
64M	Right	Right	A	S
	LAD	LAD	B1	
60M	Right	Right	A	U
	LAD	LC	C	
50M	Right	Right	B2	MI
	LAD	LAD	B1	
		LC	LC	A
62M	LAD	LAD	B2	S
58M	LC	LC	B1	S
70M	Right	Right	A	S
	LAD	LAD	B1	
51F	Right	Right	A	S
69F	LC	LC	B1	U
49M	LAD	LAD	B2	U
	LC	LC	B2	
61M	Right	Right	B2	U
	LC	LC	B2	
61M	LC	LC	B1	S
54M	Right	Right	B1	MI
54M	LC	LC	A	S
	LAD			
74F	Right	Right	A	S
Patients With Bleeding Complications				
58F	LAD	LAD	B1	U
74M	LAD	LAD	B2	S
51M	LAD	LAD	B2	U
52F	LC	LC	B1	U
57M	LAD	LAD	A	U
	LC	LC	A	
75M	Right	Right	B1	U
64M	LAD	LAD	B2	S
	LC	LC	A	
42M	LAD	LAD	B1	U
	LC	LC	A	
59M	LC	LC	A	S
	LAD	LAD	B1	
56M	LAD	LAD	A	S
	LAD	LAD	B1	
67M	Right	Right	C	S
	LAD	LAD	B1	
67M	Right	Right	B2	U
58M	LC	LC	A	S
	LC	LC	C	
			B2	
51M	Right	Right	C	U†
	LC	LC	B2	

*Diameter stenosis ≥ 50%; †no significant lesion at control angiography; ‡dissection with urgent bypass surgery.
ACC/AHA score = modified American College of Cardiology/American Heart Association Task Force score LAD = left anterior descending; LC = left circumflex; MI = after myocardial infarction; S = stable angina; U = unstable angina.

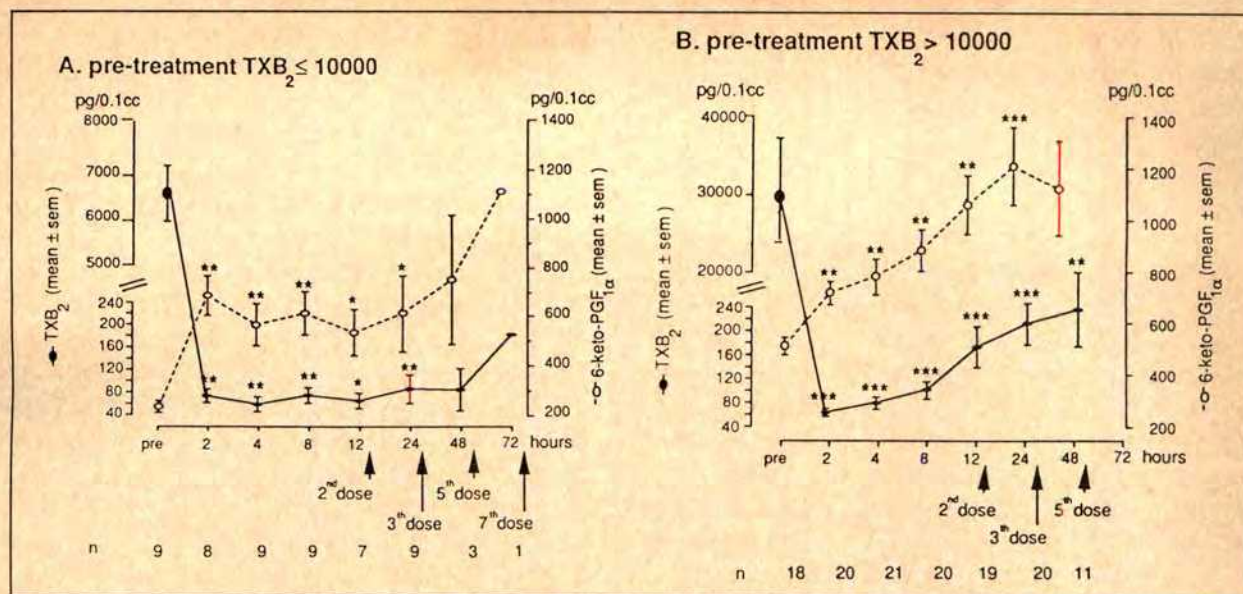


FIGURE 1. Serum thromboxane B₂ (TXB₂) (closed symbols) and 6-keto-prostaglandin F_{1α} levels (open symbols) before and after administration of ridogrel in patients with a thromboxane B₂ pre-treatment level of ≤10,000 pg/0.1 ml (A.) and >10,000 pg/0.1 ml (B.). Values are mean ± standard error of the mean. Significance versus pretreatment values was tested by a Wilcoxon test. *p < 0.05; **p < 0.01; ***p < 0.001.

dency toward hypotension (n = 3); all adverse effects were of minor clinical importance.

Serum prostanoids: Serum levels of prostanoids (thromboxane B₂ and 6-keto-prostaglandin F_{1α}) are depicted in Figure 1. Although no patient reported any aspirin or other antiplatelet drug intake for ≥10 days before the study, in nearly one-third of the patients (n = 10) a baseline serum thromboxane B₂ of ≤10,000 pg/0.1 ml was observed, suggesting a hidden nonsteroidal antiinflammatory drug consumption.¹⁵ Figure 1A depicts the serum prostanoids of patients with a thromboxane B₂ pretreatment level of ≤10,000 pg/0.1 ml, and Figure 1B those with a level of >10,000 pg/0.1 ml. In both groups, ridogrel resulted in an immediate and significant inhibition of serum thromboxane B₂ formation: thromboxane B₂ levels decreased from 6,579 ± 623 to 73 ± 12 pg/0.1 ml (p < 0.01) at 2 hours after drug administration in those with serum thromboxane B₂ ≤10,000 pg/0.1 ml at baseline, and from 29,990 ± 6,555 to 63 ± 7 pg/0.1 ml (p < 0.001) in patients with pretreatment levels of >10,000 pg/0.1 ml (p < 0.01). Serum 6-keto-prostaglandin F_{1α} increased from a pretreatment value of 232 ± 24 to 678 ± 79 pg/0.1 ml (p < 0.01) at 2 hours after intravenous ridogrel administration in patients with hidden nonsteroidal antiinflammatory drug intake, whereas an increase from 511 ± 34 to 711 ± 44 pg/0.1 ml at 2 hours and 1,190 ± 146 pg/0.1 ml at 24 hours (both p < 0.01) was observed in the other group.

Plasma concentrations of ridogrel: Plasma concentrations of ridogrel at 2, 4, 8 and 12 hours after intravenous injection of a 300-mg bolus dose were 8.80 ± 2.74, 4.56 ± 1.78, 2.00 ± 0.76 and 1.13 ± 0.52 μg/ml,

respectively (Figure 2). Plasma concentrations of ridogrel just before the third (24 hours after PTCA) and fifth (48 hours after PTCA) 300-mg dose were 2.13 ± 0.83 and 2.47 ± 0.93 μg/ml, respectively.

Follow-up results: All patients with primary successful PTCA (n = 30) were eligible for 6-month clinical follow-up. Of these, 24 (80%) patients were completely asymptomatic with a negative maximal bicycle stress test result, whereas 6 patients had recurrence of angina pectoris. Repeat coronary angiography was performed in all 6 (20%) and restenosis at the dilatation site was documented in 3, all treated with elective sur-

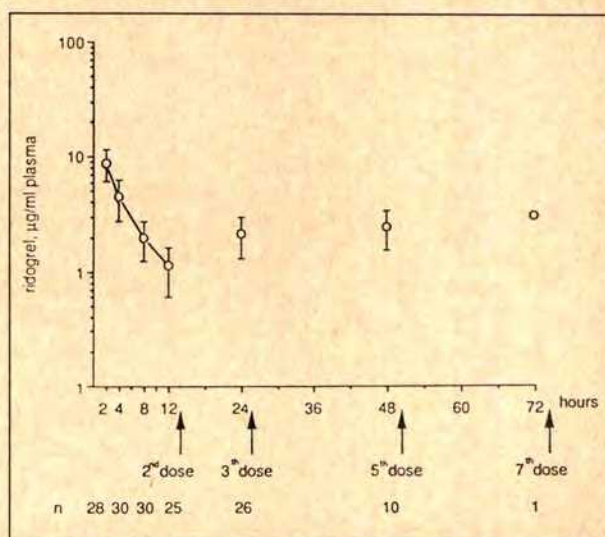


FIGURE 2. Plasma levels of ridogrel determined by high-performance liquid chromatography at various times after its administration. Values are represented as the mean ± standard error of the mean. n = the number of patients studied at the indicated time point.

gery. In the other 3 patients, no restenosis was present; however, disease progression in another segment was observed in 2 whereas in 1 patient no significant stenosis was present.

DISCUSSION

Safety: In this study, ridogrel was administered in combination with intravenous heparin to patients in whom a breach in the normally intact arterial system was present (brachial arteriotomy or femoral arterial puncture with an 8Fr introducer sheath). Because bleeding complications are known to occur in this setting even with "standard" antiplatelet therapy, a safety study with regard to untoward bleeding events appeared mandatory. In 14 (44%) of our study patients, bleeding events were noted, and almost all were related to the arterial entry site. However, most of them (11 patients) had complications of minor clinical importance; only 2 patients needed a blood transfusion. In the patient who underwent emergency bypass surgery, the increased bleeding tendency was overcome with the conventional amount of packed red cells and fresh frozen plasma.

Thus, short-term ridogrel therapy in the PTCA setting is reasonably safe. However, meticulous care of the arterial entry site during and after PTCA is mandatory in order to prevent some of the local complications.

Antiplatelet activity: The present study confirms that ridogrel is a potent, long-lasting and selective inhibitor of thromboxane B_2 synthetase. Regardless of the pretreatment value of serum thromboxane B_2 ,¹⁵ ridogrel resulted in a decrease in serum thromboxane B_2 levels, and an increase in serum 6-keto-prostaglandin $F_{1\alpha}$. Thus, even in the situation of low pretreatment thromboxane B_2 levels (residual platelet activity? newly formed platelets?), ridogrel is effective therapy.

The significant increase in serum 6-keto-prostaglandin $F_{1\alpha}$ levels (redirection of the cyclic endoperoxide metabolism) may represent an additional benefit, since experimental evidence suggests a role for antiaggregatory and vasodilatory prostaglandins acting at the injury site.⁹ Because no platelet aggregation studies were performed in this study, no judgment can be made about the potency of ridogrel as a thromboxane-prostaglandin endoperoxide receptor blocker.

Early and late restenosis: In ridogrel-treated patients, acute reocclusion did not occur. For comparison, 18 (5.6%) early acute reocclusions were present in 320 patients who underwent a PTCA procedure in the same time period in our laboratory. However, data have to be considered as observational since this study was not designed to demonstrate the effectiveness of ridogrel in preventing early acute reocclusion after PTCA. Indeed,

assuming a 6% incidence of this event using standard antiplatelet therapy, it would take a randomized study of 1,500 patients (2 groups of 750) to demonstrate a 50% reduction in this incidence with a power of 80% and $p \leq 0.05$. At long-term follow-up, 24 patients (80%) had sustained clinical success. This observational clinical restenosis rate compares favorably with patients given standard treatment in the same time period. Moreover, the complexity of the lesions that were treated in the study drug group was comparable to those in the patients given standard treatment. These facts, together with the safety data, suggest that further study of ridogrel in the setting of PTCA is justified.

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Use of a Morphologic Classification to Predict Clinical Outcome After Dissection from Coronary Angioplasty

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To determine if morphology of procedure-associated dissections could help predict clinical outcome, angiograms of 691 coronary artery dissections resulting from percutaneous transluminal coronary angioplasty were categorized according to the National Heart, Lung, and Blood Institute classification system. Classes of dissection were then correlated with clinical outcome: 543 patients with type B dissections had no increase in morbidity and mortality when compared with patients without dissection, with a similar success rate of 93.7%. Complications in this group were low and compared favorably with complication rates in procedures not associated with dissection. One hundred forty-eight procedures associated with dissections of types C to F had a significant increase in in-hospital complications, including acute closure (31%), need for emergency coronary bypass surgery (37%), myocardial infarction (13%) and repeat angioplasty (24%). The overall clinical success rate for those with types C to F dissection was 38%. The differences in clinical success and acute complications between type B and types C to F dissections were statistically significant at $p < 0.0005$ for all variables studied. The angiographic morphology of a dissection during coronary angioplasty can predict clinical outcome, aiding in selection of effective therapy.

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From its initiation in peripheral arteries, percutaneous transluminal angioplasty has been associated with intimal tears and dissections.¹ In the coronary circulation, angioplasty-related dissection confers a significant risk for major complications.² The original National Heart, Lung, and Blood Institute Registry of percutaneous transluminal coronary angioplasty found a dissection rate of 9.2%; the major complication rate in that group was 31%.³ Despite advances in knowledge and technology of the procedure, more recent registry data found a similar incidence of dissection-associated major complications.⁴ However, small dissections, in the form of intimal tears, are near ubiquitous results of angioplasty, as demonstrated by autopsy,^{5,6} and postmortem^{7,8} and animal model studies.⁹ Furthermore, dissection without complication may confer no greater risk for restenosis at the lesion site than nondissected dilations.^{10,11}

Because of its frequency of occurrence and great variation in clinical outcome, we reviewed our cases of angioplasty-associated coronary artery dissection in native coronary arteries. The angiographic morphology of each dissection was classified according to a previously proposed system.^{12,13} The different classes of dissection were then correlated with outcome, including both in-hospital complications and clinical success.

METHODS

The National Heart, Lung, and Blood Institute classification system for intimal tears, developed by the Coronary Angioplasty Registry, was chosen for classification of dissection types. The final angiographic result was scored for this study. This system grades intimal disruption based on angiographic appearance as types A to F. Type A dissections represent radiolucent areas within the coronary lumen during contrast injection, with minimal or no persistence of contrast after the dye has cleared. This was considered a nonsignificant angiographic finding after angioplasty and was not included in the study. Type B dissections are parallel tracts or double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence after dye clearance (Figure 1). Type C dissections appear angiographically as contrast outside the coronary lu-

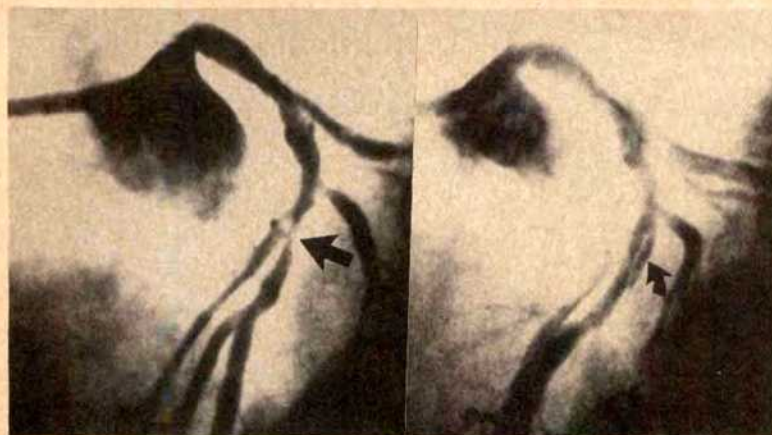


FIGURE 1. Type B dissection. Angiograms of a left anterior descending coronary artery in the left anterior oblique projection before (left) and after (right) angioplasty. Left, stenosis is seen just distal to a large septal perforating branch; right, stenosis has been successfully dilated. Injection of contrast results in a parallel tract (double lumen) separated by a radiolucent area, without contrast persistence after injection.

men, with persistence of contrast in the area after clearance of dye from the coronary lumen (Figure 2). Type D dissections represent spiral luminal filling defects, frequently with extensive contrast staining of the vessel (Figure 3). Type E dissections appear as new, persistent

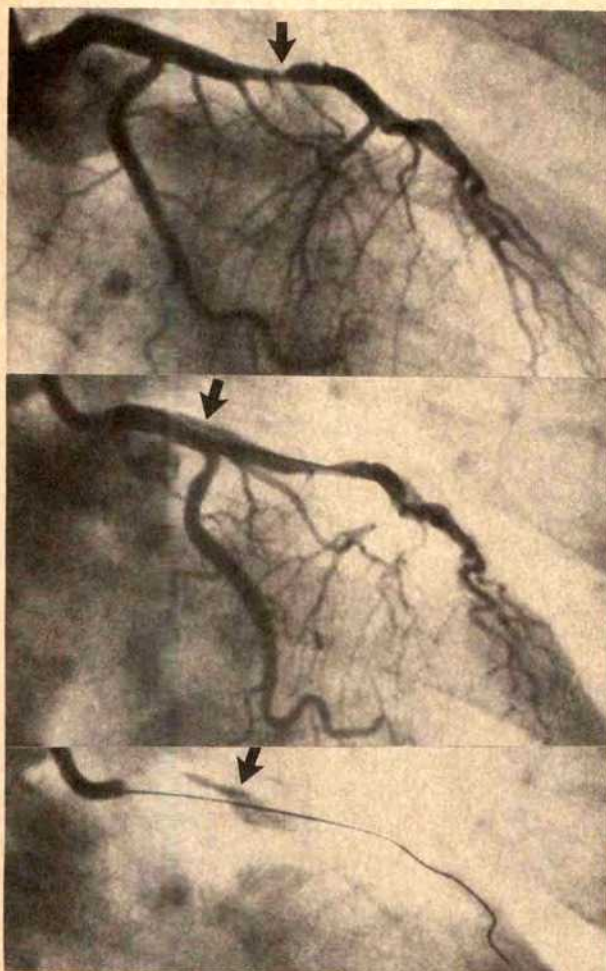


FIGURE 2. Type C dissection. Angiograms of a left anterior descending coronary artery in the right anterior oblique projection before (top) and after (middle and bottom) angioplasty. Top, stenosis is seen in the midportion of the vessel; middle, stenosis after dilation, during injection of contrast. The vessel shows the presence of an extraluminal contrast (dye cap); bottom, persistence of extraluminal dye in the area of dilation, after injection of contrast.

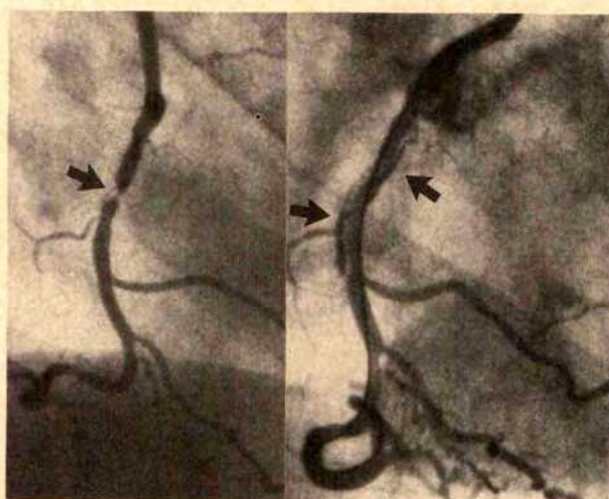


FIGURE 3. Type D dissection. Angiograms of a right coronary artery in the right anterior oblique projection before (left) and after (right) angioplasty. Left, stenosis is seen in the proximal third of the vessel; right, after dilation the vessel shows spiral dissection around the lumen of the artery. Dye flow and wash-out remain near normal.

TABLE I Patient Characteristics (9/1/87–7/17/90)

	No.	(%)
Patients with dissection	691	(32.4)
Age: mean \pm SD (yr)	61.9 \pm 10.8	
Sex		
Men	465	(67.3)
Women	226	(32.7)
Angina class*		
None	88	(12.7)
I–III	268	(38.8)
IV	335	(48.5)
PTCA coronary artery		
Right	271	(35.7)
LAD	278	(36.6)
LC	115	(15.2)
LOM	45	(5.9)
Diagonal	26	(3.4)
Patient dissection type		
B	543	(78.6)
C	62	(9.0)
D	33	(4.8)
E	18	(2.6)
F	35	(5.1)

Canadian Cardiovascular Society.
LAD = left anterior descending coronary artery; LC = left circumflex coronary artery;
LOM = left obtuse marginal; PTCA = percutaneous transluminal coronary angioplasty;
SD = standard deviation.

TABLE II Outcome After Coronary Angioplasty Dissection

	Angiographic Dissection									
	B (n = 543)		C (n = 62)		D (n = 33)		E (n = 18)		F (n = 35)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Clinical success	509	(93.7)	37	(59.7)	6	(17.6)	10	(55.6)	4	(11.4)
Emergency CABG	4	(0.7)	6	(9.7)	22	(66.7)	5	(27.8)	22	(62.9)
Abrupt reclosure	17	(3.1)	6	(9.7)	10	(30.3)	7	(38.9)	24	(68.6)
Q-wave MI	0	(0.0)	2	(3.2)	8	(24.2)	1	(5.6)	3	(8.6)
Elective CABG	15	(2.8)	10	(16.1)	4	(12.1)	2	(11.1)	1	(2.9)
Additional PTCA done	17	(3.1)	12	(19.4)	10	(30.3)	5	(27.8)	8	(22.9)

CABG = coronary artery bypass surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

filling defects. Type F dissections represent those that lead to total occlusion of the coronary artery, without distal antegrade flow. As proposed by the Coronary Angioplasty Registry, types E and F dissection may be caused by thrombus.

Angioplasty was performed during the study period by means of standard techniques. Cineangiographic films of postprocedure coronary angiography were reviewed for evidence of dissection. Dissections were then categorized using this classification system. Each case of dissection was then correlated with the patient's outcome, with respect to clinical success and in-hospital complications. Technical success was defined as <50% residual stenosis after angioplasty, and clinical success as technical success in dilating the culprit lesion plus absence of major complications or anginal pain on discharge. In-hospital complications reviewed included death, acute closure of the dilated vessel, emergency bypass surgery, myocardial infarction, elective bypass and repeat angioplasty. Elective bypass was defined as bypass surgery performed during hospitalization while the patient was clinically stable. Repeat angioplasty was angioplasty of the same lesion during the same hospitalization.

Statistical analysis: All data were analyzed using chi-square analysis and p values were determined based on comparison between groups. A p value <0.05 was accepted as statistically significant. Analyses were performed on an IBM computer using SAS statistical packages.

RESULTS

Significant dissections were noted in 691 of 2,133 procedures (32.4%) entered into our coronary angioplasty data base from November 9, 1987, until July 17, 1990. Patient characteristics and angioplasty angiographic data are in Table I. Of the 691 dissections, 543 were graded as type B (78.6%) and 148 were types C to F.

Clinical outcome and in-hospital complications were correlated with dissection type in Table II. There were

no deaths associated with dissection in any group. Success of the procedure and individual complications were noted for each of the various subgroups of dissection.

The subgroups of dissections were then compared. Statistically significant differences were found between type B dissections and all other subtypes. The results in patients with type B dissections are therefore compared with types C to F in Table III.

DISCUSSION

Intimal disruption, including angiographically apparent intimal disruption, occurs in a large percentage of vessels dilated with angioplasty. Significant disruption or dissection has been associated with a high complication rate; however, sizeable numbers of patients have excellent short- and long-term results. Because of this discrepancy, we reviewed our cases of dissection that had been prospectively classified according to a proposed schema. Our data suggest that lesions with only minimal flow disruption and no persistent staining of the vessel wall or extravasation, will likely remain open and be associated with clinical success. Conversely, complex dissections, and those with persistence of dye outside the lumen, are associated with low success rates and high percentages of in-hospital complications. These include acute reclosure, need for further revascularization in the form of bypass grafting or repeat angioplasty, and Q-wave myocardial infarction.

TABLE III Clinical Outcome in Coronary Dissection Groups

	B (n = 543)		C-F (n = 148)		p value
	No.	(%)	No.	(%)	
Clinical success	509	(93.7)	56	(37.8)	<0.0005
Emergency CABG	38	(0.7)	55	(37.2)	<0.0005
Abrupt reclosure	17	(3.1)	46	(31.1)	<0.0005
Q-wave MI	0	(0.0)	19	(12.8)	<0.0005
Elective CABG	15	(2.8)	17	(11.5)	<0.0005
Additional PTCA done	17	(3.1)	35	(23.6)	<0.0005

CABG = coronary artery bypass surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

A classification system should be an aid in ordering separate but closely related data. The National Heart, Lung, and Blood Institute schema for dissection during coronary angioplasty appears useful because the entities it distinguishes are angiographically distinct: a type C lesion is different from a type D. From the present study it is also apparent that clinical outcome and in-hospital complications differ between type B and types C to F dissections in a highly predictable fashion.

Previous studies have defined patient and angiographic variables predicting dissection before angioplasty.¹⁴⁻¹⁶ Such criteria will help interventionalists decide which lesions to avoid but are not helpful in guiding appropriate therapy once dissection has occurred. In a recent study attempting to predict ischemic events after dissection, findings included statistically significant increases in complications associated with long dissections, diameter stenoses after angioplasty of $\geq 25\%$, videodensitometric cross-sectional areas $< 2 \text{ mm}^2$, and presence of extraluminal contrast or dye "caps." The problems with these criteria include the difficulty in determining percent residual stenoses in complex dissections,¹⁸ and the lack of availability of videodensitometry in many laboratories. Furthermore, both criteria involve postprocedural analyses. Only length of dissection and extraluminal dye cap can be readily assessed in the laboratory, and are available when additional management decisions are needed. The National Heart, Lung, and Blood Institute schema is simple and can be applied immediately after dissection during the procedure.

A limitation of the proposed schema is its failure to distinguish between dissection and thrombus. This is particularly true in types E and F dissections. Although significant dissection is likely associated with thrombus due to exposure of subintimal elements, periprocedure thrombus may be managed differently than dissection.^{19,20}

Management of dissection will also be guided by clinical parameters, such as the presence of pain after the procedure and hemodynamic instability. In addition, noninvasive testing such as evolving electrocardiographic changes can also guide further management. The experienced operator will use all available data and observe all dissections in the laboratory to assure that flow and lumen size remain stable.

Dissection will likely always occur during angioplasty; it may be intrinsic to the act of dilating arteries with a balloon.^{5,8} Nonsurgical treatment methods for dissection are currently practiced or are in development and clinical trials; these include prolonged inflation with autoperfusion catheters,²¹ intracoronary stenting devices,²² laser balloon angioplasty catheters²³ and atherectomy catheters.²⁴ They may be implemented in pa-

tients with type C to F dissections as needed. Similarly, patients with type B dissections may not require the use of additional therapies. Early mobilization of surgical backup will also be aided by the schema. The National Heart, Lung, and Blood Institute classification is thus a useful tool for guiding the management of patients with dissection in the catheterization laboratory.

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Noninvasive Identification of Significant Narrowing of the Left Main Coronary Artery by Dipyridamole Thallium Scintigraphy

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To evaluate the usefulness of dipyridamole thallium scintigraphy with low-level exercise for the identification of left main (LM) coronary artery disease (CAD), 466 consecutive patients with CAD were studied. Thirty-eight patients (8%) had LM stenosis (diameter narrowing $\geq 50\%$). The LM scintigraphic pattern was present in 9 of 38 patients with LMCAD and 38 of 428 CAD patients without LMCAD (24 vs 9%; $p < 0.005$). This pattern was present in 6 of 9 patients with LMCAD without right CAD and in only 3 of 29 patients with LM and right CAD (67 vs 10%; $p = 0.0005$). Patients with LMCAD had a higher incidence of premature cessation of low-level exercise (53 vs 21%; $p < 0.0001$), chest pain (68 vs 48%; $p < 0.02$), blood pressure decrease of ≥ 20 mm Hg (44 vs 16%; $p < 0.002$) and greater ST depression (0.17 ± 0.13 vs 0.06 ± 0.10 mV; $p < 0.001$) during dipyridamole loading than patients without LMCAD. Stepwise discriminant analysis revealed that the LM scintigraphic pattern and markers of ischemia during dipyridamole loading best identified ($p < 0.0001$) patients with LMCAD without right CAD (sensitivity 67%, specificity 91%), but this predictability is no better than the LM scintigraphic pattern alone. The combination of clinical markers of ischemia during dipyridamole loading and scintigraphic findings of diffuse slow washout, extensive fixed defects and the LM pattern best identified ($p < 0.0001$) patients with LM and right CAD (sensitivity 72%, specificity 80%). These results indicate that the LM scintigraphic pattern is specific and sensitive for LMCAD without right CAD. In LM and right CAD, the predictability of this finding is low, but the addition of clinical markers of ischemia during dipyridamole loading facilitates better identification.

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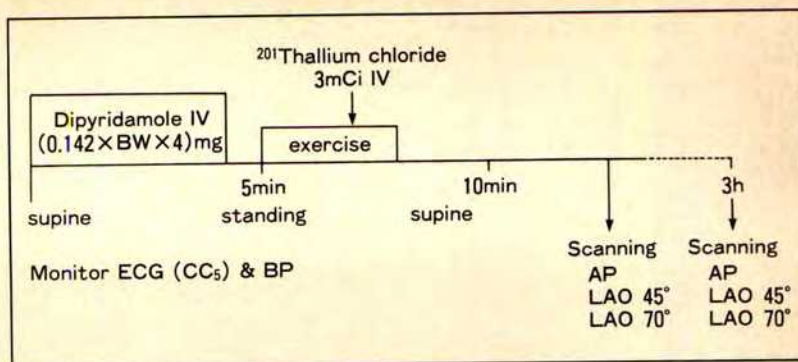
Patients with left main (LM) coronary artery disease (CAD) have poor prognosis when treated medically, but their prognosis may be improved significantly by surgical therapy.¹⁻⁵ Noninvasive identification of this particular subset of patients is therefore desirable but difficult.⁶⁻¹² Recently, dipyridamole thallium scintigraphy has been demonstrated to detect CAD with high diagnostic predictability.¹³⁻¹⁵ The present study evaluates the usefulness of scintigraphic and clinical markers of ischemia with the use of dipyridamole loading in identifying patients with LMCAD.

METHODS

Study patients: Four hundred and sixty-seven consecutive patients (364 men and 103 women) with CAD were studied. They were aged 28 to 87 years (mean 61). Two hundred and ninety-nine patients had previous myocardial infarction. LMCAD was found in 38 patients, 3-vessel CAD in 95, 2-vessel CAD in 109 and 1-vessel CAD in 224; 1 patient was excluded from the study because he developed acute myocardial infarction after dipyridamole loading. No patient after coronary artery bypass grafting was included.

Dipyridamole thallium scintigraphy: Scintigraphic study was performed within 1 week of angiography in all cases. Dipyridamole-loading thallium-201 myocardial scanning was performed ≥ 15 hours after the cessation of cardioactive medication, according to Gould's method with infusion of 0.568 mg/kg dipyridamole and walking in place for 3 minutes.^{16,17} Three mCi of thallium-201 chloride was injected during walking, and acquisition of 3 projection images (anterior, 45° left anterior oblique, 70° left anterior oblique) was begun within 5 minutes of injection using a gamma camera equipped with a high resolution collimator (Toshiba GCA401-5). Systolic blood pressure was measured using a mercury sphygmomanometer at rest, at 2 and 4 minutes after the initiation of dipyridamole injection as well as during low-level exercise (walking in place). Blood pressure response was defined as hypotensive if systolic blood pressure after low-level exercise decreased ≥ 20 mm Hg compared with the initial value. Electrocardiography and heart rate were monitored continuously using a monitoring system (Fukuda Denshi Dynascope 800) with leads in CC5 position (Figure 1).

FIGURE 1. Method of dipyridamole thallium scintigraphy. Exercise represents 3 minutes of walking in place. AP = anteroposterior projection; BP = blood pressure; BW = body weight; ECG = electrocardiography; IV = intravenous injection; LAO = left anterior oblique projection.



Scintigraphic images were acquired with 5 minutes of preset time and stored in the computer (Toshiba GMS-55A) for subsequent analysis. Identical delayed images were acquired 3 hours later. Data were analyzed using circumferential profile curve after smoothing and background subtraction of images.¹⁸ The percentage of myocardial thallium-201 washout was calculated as described previously.¹⁹ The findings were interpreted by 2 observers who were unaware of the angiographic results. Defects were classified as reversible or fixed according to conventional method.²⁰ The assignment of myocardial segments to coronary arteries is shown in Figure 2.¹⁹ Three scintigraphic findings for severe CAD were evaluated: the LM scintigraphic pattern, extensive fixed defects and diffuse slow washout.^{9-12,21-23} The LM scintigraphic pattern was defined as perfusion defects in both the left anterior descending and the circumflex coronary arterial areas,⁹⁻¹² extensive fixed defects as multiple fixed defects in ≥ 2 different areas of coronary arteries,²¹ and diffuse slow washout as washout abnormality in all myocardial segments that were related to the right, left circumflex or left anterior descending coronary artery.^{22,23} Disagreements were resolved by discussion.

Coronary angiography: Coronary cineangiography was performed in multiple oblique projections by the Judkins or the Sones technique and was interpreted using the criteria proposed by the American Heart Association.²⁴ A significant stenosis in the LM trunk was defined as $\geq 50\%$ diameter narrowing and in the 3 major coronary arteries as $\geq 75\%$.

Statistical analysis: Results are expressed as mean \pm standard deviation. A Student's *t* test was used to compare the means of the continuous variables and contingency tables were analyzed using a chi-square test. Linear discriminant analysis, with stepwise variable selection with Wilks' Lambda as the selection and optimization criteria, was used to assess the potential for correct identification. A Bayes rule with equal prior probability was used for the predictions, and results are presented as sensitivity and specificity. The statistical computations were performed using an SPSS-PC+ computer program.

RESULTS

Clinical features: Patients with LMCAD were older (65 ± 6 vs 61 ± 9 years; $p = 0.001$) and had a lesser incidence of previous myocardial infarction (42 vs 66% ; $p < 0.005$) than all the remaining CAD patients.

Scintigraphic findings: The reproducibility of interpretation of the type and the location of perfusion defects in different observers was 93%; intraobserver reproducibility was 97 and 95%. Patients with LMCAD had a higher incidence of the LM scintigraphic pattern than all the remaining patients with CAD or patients with 1-vessel CAD, whereas the incidence was similar between patients with LMCAD and those without 2- or 3-vessel CAD (Table I). A typical case with the LM

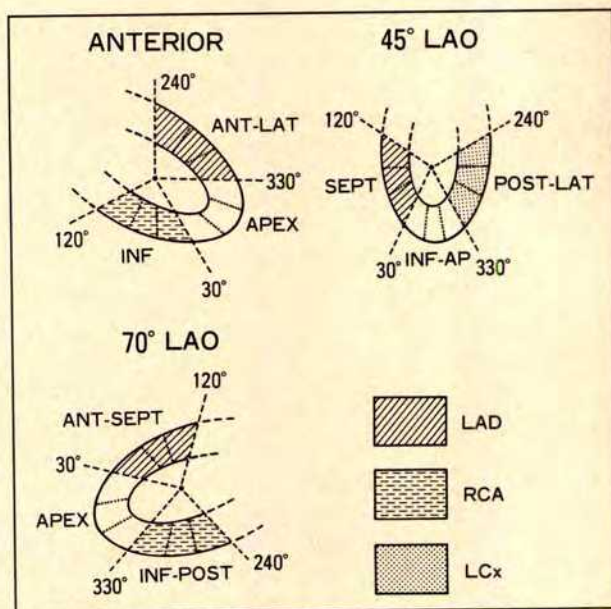


FIGURE 2. Assignment of myocardial segments to coronary arteries. The myocardium was divided into 3 segments in each projection. The segment of the myocardium from 120° to 240° in each projection was considered to represent the outflow tract and was not evaluated. In addition, the apical and inferoapical (INF-AP) regions were not assigned to a specific coronary artery because of variable overlap of different coronary arteries. ANT-LAT = anterolateral; ANT-SEPT = antero-septal; INF = inferior; INF-POST = inferoposterior segment; LAD = left anterior descending coronary artery; LAO = left anterior oblique projection; LCx = left circumflex coronary artery; POST-LAT = posterolateral segment; RCA = right coronary artery.

TABLE I Scintigraphic Findings of Severe Coronary Artery Disease

	LMCAD (n = 38)	CAD Without LMCAD (n = 428)	1VD (n = 224)	2VD (n = 109)	3VD (n = 95)
LM scintigraphic pattern	9 (24%)	38 (9%)*	6 (3%)†	18 (17%)	14 (15%)
Extensive fixed defects	4 (11)	54 (13)	11 (5)	18 (17)	25 (26)‡
Diffuse slow washout	26 (68)	132 (31)†	41 (18)†	41 (38)*	50 (53)§

*p < 0.005; †p < 0.0001; ‡p < 0.05; §p < 0.1 versus left main coronary artery disease.
CAD = coronary artery disease; LM = left main; VD = vessel disease.

TABLE II Relation Between Perfusion Defects and Coexistent Coronary Lesion(s)

Coexistent Coronary Lesion(s)	Areas of Perfusion Defects							All	Total
	ND	LMSP	LAD	LC	Right	Right + LAD	Right + LC		
None	1	2							3
LAD		1	2						3
LC		1							1
LAD + LC		2							2
Right					2				2
Right + LAD					1	3			7
Right + LC		1						1	2
3 vessels		2	1		3	7	2	3	18
Total	1	9	6		6	10	2	4	38

LAD = left anterior descending; LC = left circumflex coronary artery; LMSP = left main scintigraphic pattern; ND = no defects; Right = right coronary artery.

scintigraphic pattern was shown in Figure 3. The coexistent right coronary lesion had a significant relation to the pattern of perfusion defects in patients with LMCAD (Table II). The LM scintigraphic pattern was present in 6 of 9 patients with LMCAD without right CAD; this incidence was higher than that in patients with LM and right CAD, and 3-, 2- or 1-vessel CAD (67 vs 10, 15, 17 or 3%; $p = 0.0005$, $p = 0.0002$, $p = 0.0003$ or $p < 0.0001$; respectively) (Tables I and

II). Thus, the LM scintigraphic pattern had a sensitivity of 67% (6 of 9) and a specificity of 91% (390 of 428) for LMCAD without right CAD versus CAD without LMCAD, and a sensitivity of 10% (3 of 28) and a specificity of 91% for LM and right CAD versus CAD without LMCAD.

Clinical markers of ischemia during dipyridamole loading (Table III): Two hundred and thirty-one patients (50%) had chest pain, 182 patients (39%) had

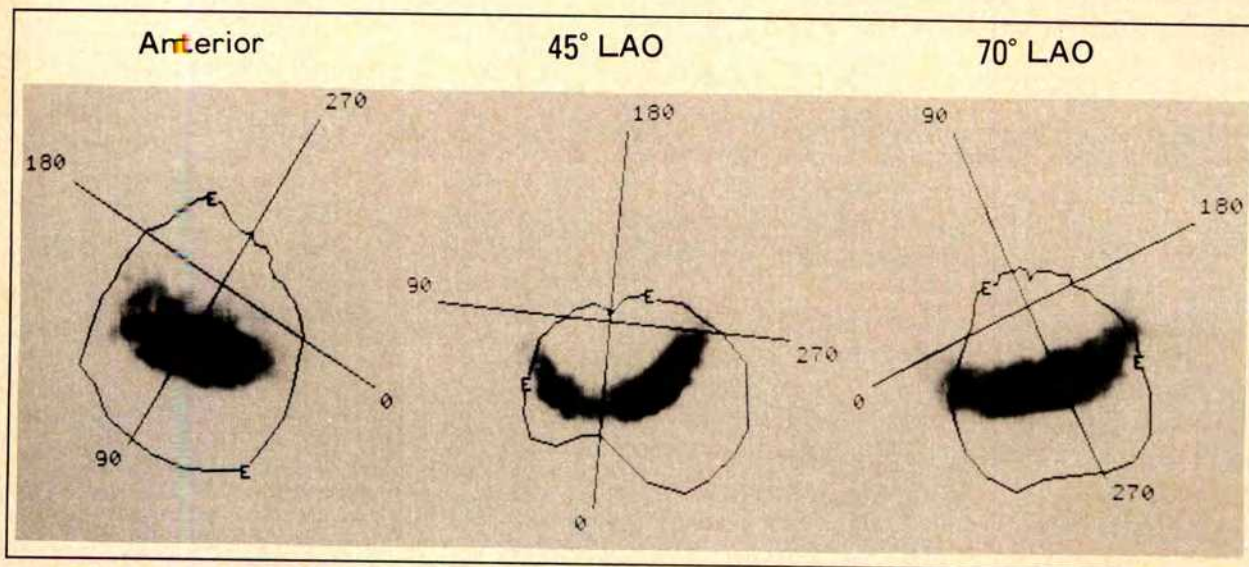


FIGURE 3. An example of perfusion defects in both the left anterior descending and left circumflex coronary arterial areas in patients with left main coronary artery disease. Coronary angiography demonstrated 90% diameter narrowing in the left main trunk, combined with 90% narrowing in the left anterior descending and complete obstruction of the left circumflex coronary artery. LAO = left anterior oblique projection.

TABLE III Clinical Markers of Ischemia and Vital Signs During Dipyridamole Loading

	LMCAD (n = 38)	CAD Without LMCAD (n = 428)	1VD (n = 224)	2VD (n = 109)	3VD (n = 95)
Completion of ex.	18 (47%)	339 (79%)*	196 (88%)†	81 (74%)‡	62 (65%)
Chest pain	26 (68)	205 (48)§	88 (39)*	57 (52)	60 (63)
ST depression (mV)	0.17 ± 0.13 (n = 18)	0.06 ± 0.10* (n = 339)	0.03 ± 0.05* (n = 196)	0.07 ± 0.08* (n = 81)	0.14 ± 0.13 (n = 62)
BP at rest (mm Hg)	139 ± 27	137 ± 22	134 ± 21	138 ± 21	143 ± 22
BP after ex. (mm Hg)	124 ± 27	133 ± 22	131 ± 22	136 ± 21	135 ± 19
Change of BP	0.90 ± 0.15	0.97 ± 0.11	0.98 ± 0.10§	0.99 ± 0.13§	0.95 ± 0.10
Hypotension	8 (44%)	53 (16%)‡	25 (13%)*	13 (16%)‡	15 (24%)
HR at rest (beats/min)	71 ± 16	71 ± 12	69 ± 11	73 ± 14	74 ± 12
HR after ex. (beats/min)	91 ± 18	94 ± 16	93 ± 15	95 ± 17	95 ± 15
Change of HR	1.30 ± 0.25	1.34 ± 0.19	1.36 ± 0.19	1.33 ± 0.19	1.31 ± 0.20
RPP (×1,000)	11 ± 3	13 ± 6§	12 ± 3	13 ± 3§	13 ± 3§

Change of BP = BP after ex./BP at rest; Change of HR = HR after ex./HR at rest. *p < 0.001, †p < 0.0001, ‡p < 0.01, §p < 0.05 versus LMCAD. BP = blood pressure; CAD = coronary artery disease; ex. = exercise; LMCAD = left main coronary artery disease; RPP = rate-pressure product; VD = vessel disease.

ST depression of ≥ 0.1 mV, and 199 patients (43%) needed aminophylline to reverse the adverse effects of dipyridamole. Patients with LMCAD had a higher incidence of chest pain than those with 1-vessel CAD and greater ST depression than those with 1- or 2-vessel CAD. Three hundred and fifty-seven patients (77%) completed low-level exercise, whereas 109 patients (23%) could not complete the exercise due to chest pain, dyspnea or faintness; the incidence of premature cessation of this low-level exercise was higher in patients with LMCAD than in the remaining patients with CAD. In 357 patients who completed the exercise, hypotension induced by dipyridamole was seen more often in patients with LMCAD than in those with 1-, 2- or 3-vessel CAD, whereas heart rate at rest and after the exercise and blood pressure at rest were similar in each group. When patients were considered at high risk during dipyridamole loading if they could not complete low-level exercise or had hypotension, more patients with LMCAD had this high-risk parameter than those with 1-, 2- or 3-vessel CAD (28 of 38 vs 53 of 224, 41 of 109 or 48 of 95; $p < 0.0001$, $p = 0.0001$ or $p < 0.02$; respectively).

Multivariate analysis for identification of left main coronary artery disease: The following 9 variables were considered potential predictors for identifying LMCAD and were entered into a stepwise discriminant analysis: age, gender, previous myocardial infarction, chest pain, ST depression and the high-risk parameter during dipyridamole loading, extensive fixed defects, diffuse slow washout and the LM scintigraphic pattern. Multivariate analysis in 437 patients after excluding 29 patients with LM and right CAD revealed that the combination of the LM scintigraphic pattern, previous myocardial infarction, gender, the high-risk parameter and chest pain during dipyridamole loading was most statistically significant ($p < 0.0001$) in identifying LMCAD without right CAD (sensitivity 67%,

specificity 91%). But this predictability was no better than the LM scintigraphic pattern alone. The analysis was repeated in 457 patients after excluding 9 patients with LMCAD without right CAD. This revealed that the combination of ST depression, diffuse slow washout, the high-risk parameter during dipyridamole loading, the LM scintigraphic pattern, extensive fixed defects and chest pain was most statistically significant ($p < 0.0001$) in identifying LM and right CAD (sensitivity 72%, specificity 80%). The analysis was also repeated using 95 patients with 3-vessel CAD and 29 patients with LM and right CAD. This revealed that the combination of the high-risk parameter during dipyridamole loading, previous myocardial infarction, diffuse slow washout and extensive fixed defects was the best ($p = 0.012$) predictor for identifying LM and right CAD (sensitivity 69%, specificity 61%).

DISCUSSION

This study demonstrated low sensitivity (24%) and high specificity (91%) of the LM scintigraphic pattern to identify LMCAD in 466 consecutive patients with CAD. Previous studies also reported low sensitivity of 13 to 14% of this scintigraphic pattern, which was considered due to coexistent coronary lesions with more critical stenosis than the LM lesion.^{10,11} Higher sensitivity of this scintigraphic pattern in the present study may originate from differences in study population but may also be related to dipyridamole loading, which enables adequate stress in patients who cannot or will not exercise properly.^{25,26} The analysis of the relation between coexistent coronary lesions and pattern of perfusion defects revealed that right CAD played an important role; 6 of 9 patients with LMCAD without right CAD had the LM scintigraphic pattern and only 3 of 29 patients with LM and right CAD had this scintigraphic pattern, although these values were based on a rather small number of patients. Because scintigraphic

imaging is relative,^{10,19} perfusion defects in the area of the right coronary artery may obliterate the existence of defects in the area of the left anterior descending or circumflex arteries, or both. Thus, the LM scintigraphic pattern was infrequently found in patients with LM and right CAD. In contrast, in patients with LMCAD without right CAD, this LM scintigraphic pattern was a single and the best predictor.

The incidence of chest pain and ischemic ST depression induced by dipyridamole was higher in our study compared with a previous report on 3,911 patients, in which 19.7% of the patients had chest pain and 7.5% had ST depression.²⁷ However, only 28% of the patients had coronary angiography and dipyridamole thallium scintigraphy within a 1-year period and there was no uniform protocol or standard procedure in the previous study. In contrast, in the present study all patients underwent both angiographic and scintigraphic studies within a week using the same protocol and all had angiographic CAD. These differences in study population and design may account for a different incidence of chest pain and ST depression. The higher incidence of chest pain and dipyridamole-induced hypotension and the greater magnitude of ST depression in patients with LMCAD is of interest. Blood pressure decrease during exercise testing was reported to occur in 5 to 11% of patients with CAD, and was regarded as a sign of multiple vessel CAD.^{28,29} Our study demonstrated that dipyridamole-induced hypotension was also a marker of severe CAD. A higher incidence of hypotension during dipyridamole loading, compared with exercise testing, may be due to the potent vasodilator effect of dipyridamole.^{15,17}

When clinical markers of ischemia during dipyridamole loading and scintigraphic findings of severe CAD were used, the identification of patients with LM and right CAD was possible, although the predictability of the LM scintigraphic pattern alone was very low. Considering the results yielded by the combination of non-specific markers of severe CAD, one might suspect that the statistical power might heavily depend on the low incidence of clinical and scintigraphic markers of severe CAD in patients with 1- or 2-vessel CAD. However, the fact that the multivariate analysis could differentiate LMCAD from 3-vessel CAD suggests that this was not the case. Nygaard et al¹¹ reported successful identification of LMCAD with the use of both exercise thallium scintigraphy and electrocardiographic exercise testing. Our study indicates that the analysis of scintigraphic findings together with the assessment of clinical markers of ischemia during dipyridamole loading facilitates the identification of LMCAD by a single examination.

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Evaluation of Dipyridamole-Doppler Echocardiography for Detection of Myocardial Ischemia and Coronary Artery Disease

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Doppler assessment of left ventricular filling and ejection during dipyridamole stress may supplement wall motion analysis for detection of myocardial ischemia and coronary artery disease (CAD). Thirty-four patients taking no cardioactive therapy were studied using intravenous dipyridamole (0.6 mg/kg) during 2-dimensional and pulsed Doppler echocardiography. Twelve patients had normal coronary arteries (group 1) and the remainder, who had significant CAD, were divided into groups 2 (n = 11) and 3 (n = 11). Only subjects in group 2 developed myocardial ischemia manifest as reversible regional asynergy and ST-segment depression. Heart rate increased (16 ± 9 beats/min, $p < 0.01$) and mean blood pressure decreased (-5 ± 8 mm Hg, $p =$ not significant) uniformly across groups. Exaggerated hyperkinesia of normally contracting wall segments was the common response to dipyridamole infusion in patients with CAD. The respective mean percent changes in peak early diastolic velocity, peak atrial velocity, their ratio and ejection peak velocity, and mean acceleration for groups 1 (20, 42, -13, 20 and 23%), 2 (22, 32, -2, 10 and 14%) and 3 (23, 33, -6, 16 and 18%) were similar. Comparisons between normal patients and those with CAD and between groups 2 and 3 revealed no significant differences in the effect of dipyridamole on any variable. However, a decrease in both peak velocity and mean acceleration of left ventricular ejection was seen in 3 of 4 group 2 patients who developed severe ischemia. Dipyridamole-Doppler echocardiography is insensitive for detection of CAD and appears unable to identify myocardial ischemia unless this is severe. Hemodynamic

changes and compensatory wall motion induced by dipyridamole may explain these findings.

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Doppler interrogation of intracardiac flow is useful in assessing global left ventricular systolic function¹ and gives insight into diastolic function.^{2,3} Measurement of aortic blood flow velocity and acceleration has been used to detect exercise-induced ischemic left ventricular dysfunction in patients with coronary artery disease (CAD), but this approach appears limited by tachycardia and patient motion.⁴ Myocardial ischemia causes acute impairment in left ventricular relaxation and alterations in the mitral inflow velocity curve, which appears to occur earlier and to be a more sensitive indicator of ischemia than evidence of systolic dysfunction.⁵ Intravenous dipyridamole stress is an alternative to exercise that has been combined with 2-dimensional echocardiography,⁶ but evidence of its value in conjunction with Doppler transmitral and transaortic flow variables is conflicting.⁷⁻¹¹ Doppler data could potentially be combined with wall motion analysis to enhance the use of dipyridamole stress echocardiography in evaluating patients with CAD. Therefore, this prospective study was designed to assess the usefulness of dipyridamole-Doppler echocardiography in diagnosing CAD and detecting myocardial ischemia.

METHODS

Study patients: Thirty-four patients (mean age \pm standard deviation 56 ± 9 years, range 42 to 71; 25 men and 9 women) complaining of chest pain were studied. Patients with severely impaired left ventricular function, left ventricular hypertrophy, syndrome X, valvular heart disease, bronchospasm and bundle branch block or ≥ 1 mm of ST-segment deviation from isoelectric were excluded. All subjects were in sinus rhythm and were divided into 3 groups on the basis of coronary anatomy and response to dipyridamole (Table I). Patients in group 1 had normal coronary arteries and left ventricular function at cardiac catheterization, and had no evidence of myocardial ischemia after dipyridamole administration. Those in groups 2 and 3 had significant

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CAD. All group 2 patients had exertional angina pectoris, a positive exercise electrocardiogram, and dipyridamole-induced myocardial ischemia by electrocardiographic criteria (≥ 1 mm of planar or downsloping ST-segment depression 80 ms after the J point compared with baseline) and 2-dimensional echocardiographic criteria (new or worsening regional asynergy).¹² Patients in group 3 had no evidence of ischemia after dipyridamole stress. The respective numbers of patients with 1-, 2- and 3-vessel disease were 0, 7 and 4 in group 2, and 3, 4 and 4 in group 3. All patients gave informed consent and the study was approved by the hospital ethics committee.

Study protocol: Patients were instructed to avoid tea and coffee on the day of the test and had discontinued all cardioactive treatment for 4 half-lives beforehand. Baseline heart rate and blood pressure were determined (Critikon, Dinamap vital signs monitor), and 12-lead electrocardiogram, 2-dimensional echocardiogram with color-flow mapping and Doppler study were performed. Pediatric-size chest electrodes were used to maximize the window available for echocardiography. During continuous electrocardiographic monitoring, intravenous dipyridamole (0.6 mg/kg) was given over 5 minutes. Hemodynamics, 12-lead electrocardiography and pulsed Doppler interrogation of left ventricular filling and ejection were recorded every 1 to 2 minutes up to 30 minutes after dipyridamole infusion. Two-dimensional echocardiographic monitoring was continuous except during Doppler evaluation. Parasternal long-axis, short-axis and apical 4- and 2-chamber views were obtained using a Toshiba SSH-160A scanner and 3.75-MHz transducer. All studies were recorded on 12-mm VHS videotape for subsequent analysis. An 11-segment left ventricular model was used for wall motion analysis. Echocardiograms were read at baseline and peak stress, and each segment was graded as hyperkinetic, normal, hypokinetic, akinetic or dyskinetic. Electrocardiograms and 2-dimensional echocardiograms were interpreted by 1 of 2 independent observers without knowledge of the clinical or Doppler findings.

Doppler examination and analysis: Pulsed Doppler recordings were obtained from the apical window using a 2.5-MHz transducer and sample volume positioned at the mitral leaflet tips and in the left ventricular outflow tract during midexpiratory apnea. Transducer angulation and sample volume location were adjusted to obtain an optimal signal. Peak early diastolic velocity, peak atrial velocity, their ratio, and the peak velocity and mean acceleration of ventricular outflow, together with the corresponding heart rates, were determined at baseline and during ischemia or peak effect 3 to 5 minutes after drug administration by 1 of 2 independent observers unaware of patient data. The modal velocity was used throughout and data from 3 representative

TABLE I Baseline Characteristics of Study Group

	Group 1	Group 2	Group 3	p Value	
				Group 1 vs 2 and 3	Group 2 vs 3
No. of pts.	12	11	11	—	—
Age (yr)	54 \pm 10	58 \pm 8	57 \pm 8	NS	NS
EF (%)	68 \pm 7	64 \pm 11	62 \pm 8	NS	NS
LVEDP (mm Hg)	12 \pm 3	15 \pm 6	14 \pm 6	NS	NS
HR (beats/min)	71 \pm 15	76 \pm 10	72 \pm 11	NS	NS
MBP (mm Hg)	106 \pm 9	110 \pm 13	109 \pm 14	NS	NS

EF = ejection fraction; HR = heart rate; LVEDP = left ventricular end-diastolic pressure (after a wave); MBP = mean blood pressure; NS = not significant.

beats of high quality were averaged. Aminophylline was given, when necessary, after complete collection of Doppler data. Baseline variability was determined from 2 Doppler recordings taken 5 minutes apart in 20 patients. Interobserver variability was assessed from 40 pairs of values for each parameter measured. Intraobserver variability was determined similarly, without knowledge of the first evaluation.

Cardiac catheterization: All patients underwent coronary arteriography and left ventriculography. A diameter reduction $\geq 70\%$ in a major epicardial vessel was considered significant. Percent ejection fraction, calculated by the area-length ellipsoid method,¹³ was determined using the computer-assisted Cardiovascular Angiography Analysis System (Pie Data Medical) by manual tracing of the end-diastolic and end-systolic frames of the left ventriculogram recorded on 35-mm cinefilm (Table I).

Statistical analysis: Values are summarized as mean \pm standard deviation. Paired data were evaluated using the paired *t* or Wilcoxon test, as appropriate, and group comparisons were done using 1-way analysis of variance with orthogonal contrasts. Correlation coefficients were calculated to determine the effects of changes in hemodynamics on Doppler measurements. Variability is expressed as percent coefficient of variation. A *p* value <0.05 was considered statistically significant.

RESULTS

Baseline findings and data variability: Table I reveals that pretest ejection fraction, left ventricular end-diastolic pressure, heart rate and mean blood pressure were not significantly different between groups. Regional asynergy on 2-dimensional echocardiography was present in no patient in group 1, 6 in group 2 and 5 in group 3. The total number of segments with abnormal wall motion was 13 in group 2 and 12 in group 3. A trace (*n* = 6) or mild (*n* = 3) mitral regurgitation was present in 9 patients (26%) during color-flow mapping; no patient had aortic regurgitation. Doppler vari-

TABLE II Baseline, Interobserver and Intraobserver Variability for the Measured Doppler Parameters

	Baseline Variability (%)	Interobserver Variability (%)	Intraobserver Variability (%)
Peak early velocity	9	7	5
Peak atrial velocity	10	7	6
E/A ratio	10	8	6
Ejection peak velocity	8	5	5
Ejection mean acceleration	10	8	7

Data are expressed as percent coefficient of variation.
E/A = peak early to atrial filling velocity.

ables were not significantly different between groups, with 2 exceptions. First, the peak early diastolic velocity was higher in group 1 than in groups 2 and 3 (0.74 ± 0.15 vs 0.56 ± 0.16 m/s) ($p < 0.01$). Second, the peak early to atrial velocity ratio was also higher in group 1 than in groups 2 and 3 (1.46 ± 0.40 vs 1.00 ± 0.28 , $p < 0.01$). Patients with CAD and regional asynergy ($n = 1$) had similar values for all Doppler parameters compared with those with normal wall motion

($n = 11$) (all $p =$ not significant [NS]). Baseline variability was greater than interobserver and intraobserver variability (Table II).

Doppler variables and influence of hemodynamics:

Mean increases in heart rate for the 3 groups were 17 ± 7 , 15 ± 11 and 16 ± 7 beats/min, respectively (all $p < 0.01$). For the entire study group, changes in peak atrial velocity and peak early to atrial velocity ratio during dipyridamole stress correlated significantly with change in heart rate; the other 3 Doppler variables were not so related. The correlation was strongly positive for peak atrial velocity ($r = 0.84$, $p < 0.001$) and negative for peak early to atrial velocity ratio ($r = -0.57$, $p < 0.001$), and was similar for all 3 groups. Tachycardia after dipyridamole caused fusion of early and atrial waves in 2 patients in group 1 and 1 patient in group 2, rendering analysis of transmitral flow impossible in these patients. Heart rate increased by 20, 22 and 29 beats/min, respectively, during these studies. The mean decreases in mean blood pressure were -6 ± 4 , -6 ± 14 and -3 ± 3 mm Hg in groups 1, 2 and 3, respec-

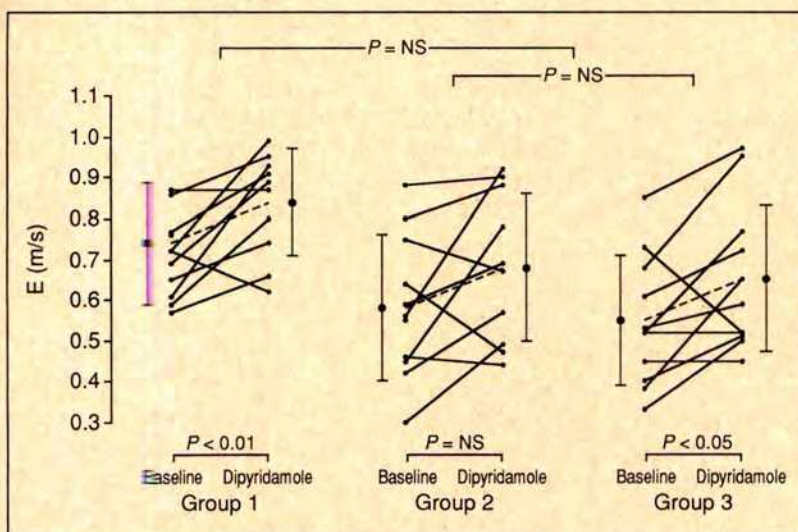


FIGURE 1. Individual, mean and standard deviation data for peak early filling velocity (E) measured at baseline and peak stress for groups 1, 2 and 3. Significance values within and between groups are also shown. Three missing data points. NS = not significant.

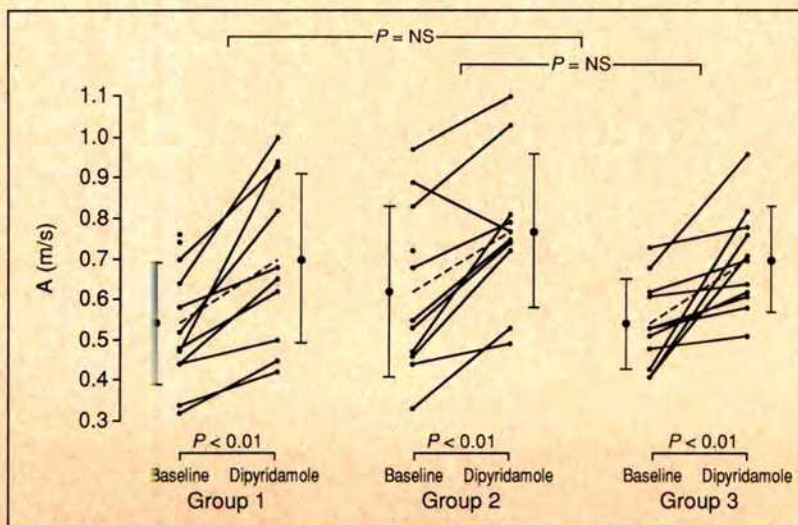


FIGURE 2. Individual, mean and standard deviation data for peak atrial filling velocity (A) measured at baseline and peak stress for groups 1, 2 and 3. Significance values within and between groups are also shown. Three missing data points. NS = not significant.

tively. No significant correlation was found between change in any Doppler variable and change in systolic, diastolic or mean blood pressure.

Detection of coronary artery disease: In group 1 the effect of dipyridamole on peak early velocity (0.74 ± 0.15 to 0.84 ± 0.13 m/s, $p < 0.01$), peak atrial velocity (0.54 ± 0.15 to 0.70 ± 0.21 m/s, $p < 0.01$), peak early to atrial velocity ratio (1.46 ± 0.40 to 1.29 ± 0.40 , $p = \text{NS}$), ejection peak velocity (0.82 ± 0.15 to 0.97 ± 0.13 m/s, $p < 0.001$) and mean acceleration (9.62 ± 2.17 to 11.69 ± 2.55 m/s², $p < 0.01$) is shown in Figures 1 to 5. The changes in patients with CAD ($n = 22$) were 0.56 ± 0.16 to 0.68 ± 0.18 m/s ($p < 0.05$), 0.58 ± 0.17 to 0.73 ± 0.16 m/s ($p < 0.01$), 1.00 ± 0.28 to 0.93 ± 0.29 ($p = \text{NS}$), 0.77 ± 0.14 to 0.86 ± 0.15 m/s ($p < 0.05$), and 8.82 ± 1.59 to 10.21 ± 2.30 m/s² ($p < 0.05$), respectively (group 1 vs groups 2 and 3, all $p = \text{NS}$). The corresponding mean percent changes in these Doppler variables in group 1 (20, 42, -13, 20 and 23%) and groups 2 and 3 (23, 33, -4, 13 and

16%) also did not differ significantly. Ejection peak velocity and mean acceleration were the most discriminatory parameters. When an abnormal response was defined as an absolute decrease in these variables, the sensitivity and specificity for detection of CAD using peak velocity was 18 and 82%, and using mean acceleration 18 and 100%. Individual patients in all 3 groups showed highly variable responses to dipyridamole infusion (Figures 1 to 5).

Detection of myocardial ischemia: Hyperkinetic wall motion was the characteristic response to dipyridamole, and exaggerated hyperkinesia of normal wall segments was frequently seen in patients with CAD. Positive electrocardiographic changes and new ($n = 6$) or worsening ($n = 6$) wall motion abnormalities were seen in all 11 subjects in group 2. One patient had both new and worsening regional asynergy, and another developed transient left ventricular cavity dilation associated with extensive anterior akinesia. For group 2, changes in peak early velocity (0.58 ± 0.18 to 0.68 ± 0.18 m/

FIGURE 3. Individual, mean and standard deviation data for peak early to atrial velocity (E/A) ratio measured at baseline and peak stress for groups 1, 2 and 3. Significance values within and between groups are also shown. NS = not significant.

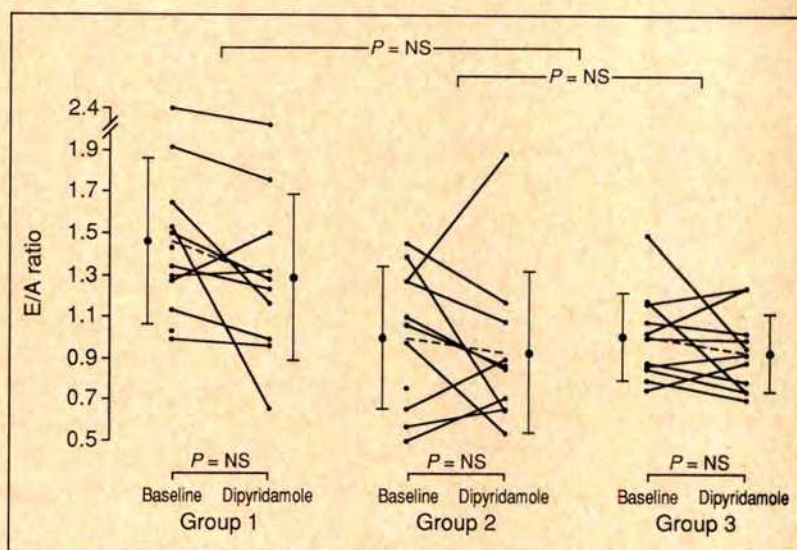
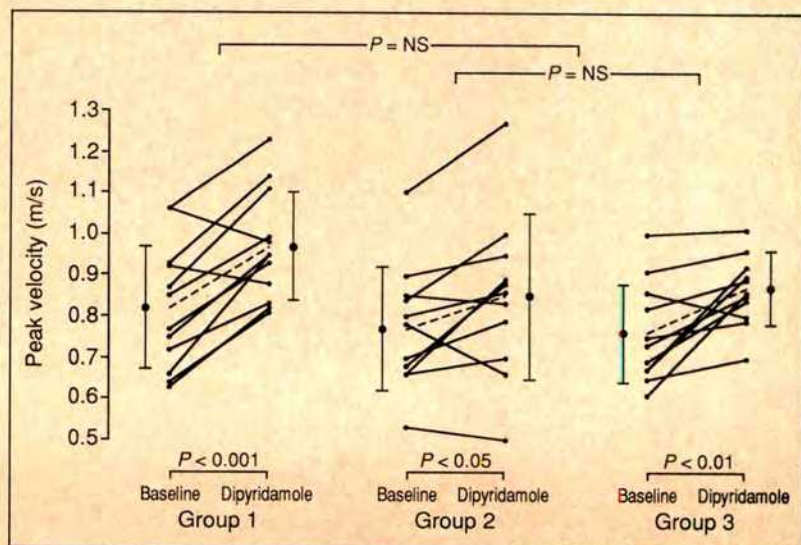


FIGURE 4. Individual, mean and standard deviation data for peak velocity of left ventricular ejection measured at baseline and peak stress for groups 1, 2 and 3. Significance values within and between groups are also shown. NS = not significant.



s), peak atrial velocity (0.62 ± 0.21 to 0.77 ± 0.19 m/s), peak early to atrial velocity ratio (1.00 ± 0.34 to 0.93 ± 0.35), ejection peak velocity (0.77 ± 0.15 to 0.85 ± 0.20 m/s) and mean acceleration (9.00 ± 1.46 to 10.26 ± 2.56 m/s²) are shown in Figures 1 to 5. Equivalent findings in group 3 were 0.55 ± 0.16 to 0.65 ± 0.18 m/s, 0.54 ± 0.11 to 0.70 ± 0.13 m/s, 1.01 ± 0.21 to 0.93 ± 0.19 , 0.76 ± 0.12 to 0.87 ± 0.09 m/s and 8.64 ± 1.77 to 10.15 ± 2.13 m/s², respectively (group 2 vs 3, all $p = \text{NS}$). The corresponding mean percent changes in these Doppler variables in groups 2 (22, 32, -2, 10 and 14%) and 3 (23, 33, -6, 16 and 18%) also did not differ significantly. Four group 2 patients had new akinesia or dyskinesia involving ≥ 2 segments associated with ≥ 2 -mm ST-segment depression. Although changes in Doppler transmitral flow variables in these patients were not dissimilar from the rest, both peak velocity and mean acceleration of left ventricular ejection decreased in 3 of the 4.

DISCUSSION

Some patients with suspected CAD are unable or poorly motivated to undergo an exercise test. Intravenous dipyridamole can induce myocardial ischemia in persons with significant CAD that manifests as transient regional asynergy on 2-dimensional echocardiography.¹⁴ This represents an alternative stress test in these patients, but appears to have a sensitivity somewhat less than dipyridamole perfusion imaging.¹⁵ Evidence that Doppler data might improve sensitivity comes from a number of sources. The peak velocity and acceleration of aortic flow have been found to decrease during experimental coronary occlusion in dogs.¹⁶ In addition, decreases in peak early diastolic velocity and peak early to atrial velocity ratio, and compensatory increase in peak atrial velocity have been reported dur-

ing ischemia induced by balloon inflation during coronary angioplasty in patients with CAD.^{5,17} We therefore studied patients with normal coronary arteries (group 1) and with CAD, both with (group 2) and without (group 3) inducible ischemia, to determine the utility of this approach. Subjects with syndrome X were excluded because of evidence suggesting they may have regional impairment of maximal coronary vasodilator reserve in response to dipyridamole.¹⁸ No patient in group 1 developed evidence of myocardial ischemia after dipyridamole administration. The 3 groups were well-matched for age, left ventricular systolic function and baseline hemodynamics (Table I), and all were off cardioactive therapy.

Baseline variability, which is highly relevant in studies involving serial Doppler data acquisition, was greater than interobserver and intraobserver variability (Table II). This measure incorporates intraobserver variability, physiologic variation and technical variation due to slightly different sample volume location and alignment with blood-flow direction on serial interrogation.¹⁹

Intravenous dipyridamole causes systemic vasodilation and a secondary increase in heart rate, stroke volume and cardiac index.²⁰ Left ventricular filling pressure, and peak positive and negative left ventricular dP/dt all increase significantly.^{20,21} Invasive studies have shown that both reductions in afterload and elevations in preload increase Doppler transaortic flow indexes^{22,23} and peak early filling velocity.²⁴ The observation that peak atrial velocity increases during exercise and correlates significantly with heart rate²⁵ parallels our own observations. Therefore, hemodynamic effects probably account for the increases in peak early, peak atrial and ejection peak velocities, and mean acceleration we found in group 1. The peak early to atrial velocity ratio is clearly influenced by changes in its com-

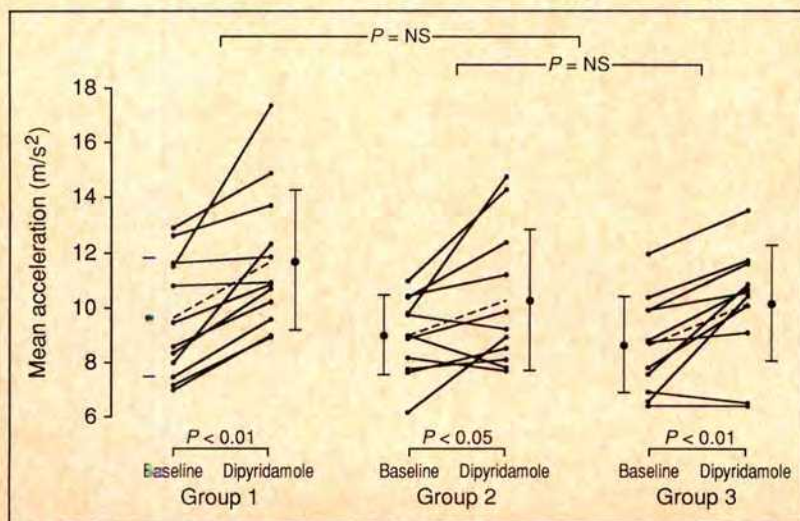


FIGURE 5. Individual, mean and standard deviation data for mean acceleration of left ventricular ejection measured at baseline and peak stress for groups 1, 2 and 3. Significance values within and between groups are also shown. NS = not significant.

ponents and tended to decrease, although nonsignificantly, because of a greater increase in peak atrial velocity.

Doppler left ventricular ejection indexes: Studies to determine whether Doppler interrogation of aortic flow can reliably detect reversible perfusion abnormalities on dipyridamole-thallium scintigraphy are limited by the uncertain relation between perfusion defects, which may only be relative, and myocardial ischemia.^{7,9} Labovitz et al⁷ reported that changes in aortic flow variables during dipyridamole infusion increased the sensitivity of 2-dimensional echocardiography in the detection of CAD, from 64 to 85%, but did not state whether antianginal treatment was discontinued before dipyridamole infusion. Beta blockade, in particular, considerably alters Doppler ejection dynamics²⁶ and may have accounted for the failure of aortic peak velocity and acceleration to increase after dipyridamole infusion in this study.⁷ Harrison et al⁴ noted increases in Doppler indexes of aortic flow with exercise in nearly all patients despite the presence of myocardial ischemia. Our findings are consistent with this observation. The inability of baseline Doppler data to identify patients with pretest regional asynergy is consistent with no significant differences in the response to dipyridamole between groups. The decrease in systemic vascular resistance^{20,22,23} and exaggerated hyperkinesia of normal wall segments, frequently observed in our patients with CAD, may explain these disappointing results. However, 3 of 4 patients with severe ischemia by echocardiographic and electrocardiographic criteria had a decrease in both peak velocity and mean acceleration, suggesting a failure of compensatory wall motion in these patients.

Doppler left ventricular filling indexes: Alterations in left ventricular chamber stiffness and relaxation have opposing effects on the pattern of transmitral flow.^{3,27} Patients with CAD in this study had a reduced peak early velocity and peak early to atrial velocity ratio at baseline, implying abnormal relaxation.^{3,27} This makes between group comparisons of changes induced by dipyridamole harder to interpret. Preload,²⁴ afterload, heart rate²⁵ and age²⁸ all significantly influence this flow profile, and early and atrial filling are, in large measure, interdependent.²⁷ In our patients, change in heart rate correlated significantly and uniformly across groups, with change in both peak atrial velocity and peak early to atrial velocity ratio. Furthermore, fusion of early and atrial waves with tachycardia confounded analysis of transmitral flow in 3 of 34 patients (9%). Therefore, left ventricular filling is influenced by a complex interplay of multiple factors, and cannot be directly equated with diastolic function. We found that

transmitral flow variables changed similarly in all 3 groups during dipyridamole stress, suggesting that hemodynamic influences predominated. Elevated preload and reduced afterload may well have masked the expected consequences of myocardial ischemia on the velocity profile in group 2.^{5,24} Doppler variables were similarly insensitive on subgroup analysis of patients with severe ischemia. These findings are consistent with those of Grayburn et al,⁹ although other studies have reached less clear conclusions.^{10,11} The observation that individual patients showed highly variable responses to dipyridamole infusion perhaps reflects the multiplicity of determinants of Doppler filling dynamics.

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Pronounced Reduction of Aortic Flow Velocity and Acceleration During Heavy Isometric Exercise in Coronary Artery Disease

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Doppler-derived parameters of aortic flow were examined during heavy isometric exercise in 48 men with coronary artery disease (CAD) and in 48 gender- and age-matched healthy controls. The aim was to determine which parameters best separated the groups and to look for a possible relation between exercise-induced Doppler patterns and the extent of CAD. Isometric exercise was performed with a 2-hand bar dynamometer, and the subjects were required to perform 50% of maximal voluntary contraction for 2 minutes. Examination was performed with a pulsed Doppler transducer positioned at the suprasternal notch. Resting peak flow velocity, acceleration time, stroke volume index and cardiac index did not show significant differences between the groups. However, mean acceleration and stroke work were significantly lower in patients with CAD. In this group, exercise peak flow velocity decreased from 98 ± 13 to 55 ± 12 cm/s, flow velocity integral from 14 ± 3 to 7 ± 3 cm, mean acceleration from 11 ± 0.9 to 4.7 ± 1 m/s/s, and stroke volume index from 41 ± 6 to 23 ± 4 ml/m² ($p < 0.001$ for all). Cardiac index decreased from 2.7 ± 0.4 to 2 ± 0.2 liters/min/m² ($p < 0.05$). Acceleration time increased from 82 ± 6 to 116 ± 7 ms. In most of the indexes, the directional changes induced by isometric exercise were similar in patients with CAD and in normal control subjects. The differences compared with the rest values were significantly greater in the CAD group, and especially in patients presenting with 3-vessel disease. In conclusion, isometric exercise results in marked changes in aortic flow patterns both in normal subjects and in subjects with CAD. Exercise-induced changes in peak flow velocity and mean

acceleration were found to best separate the groups, and the degree of reduction in their values was directly related to the extent of CAD.

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Doppler echocardiography is a useful tool for assessing left ventricular function at rest. Its accuracy in estimating stroke volume and cardiac output was shown in experimental¹ and human studies.^{2,3} In addition, this technique can detect exercise-induced changes in aortic flow velocity in normal subjects⁴⁻⁶ and in patients with coronary artery disease (CAD).^{7,8} The cardiovascular responses to isometric exercise are characterized by an increase in systolic and diastolic blood pressures with modest elevation of heart rate. This type of exercise has been used for evaluating left ventricular function in both healthy⁹ and sick¹⁰ patients. Most exercise Doppler studies used dynamic exercise — either in the supine^{4,6} or upright position^{5,7,8} — or relatively light isometric exercise.¹¹ Little data are available on the influence of heavy isometric exercise on Doppler-derived indexes of aortic flow. The present study (1) determines the effects of heavy isometric exercise on Doppler-derived parameters of aortic flow in healthy persons and patients with CAD, (2) determines which parameter best separates the groups, and (3) inquires into a possible relation between the exercise-induced Doppler patterns and the extent of CAD.

METHODS

Subject group: The study consisted of 2 groups. Group A comprised 48 healthy untrained men, aged 39 to 54 years (mean \pm standard deviation 48 ± 6), referred for periodical check-up in the framework of our primary prevention program. They had no history of cardiovascular disease and no known risk factors for the development of CAD. All had normal findings on physical examination, standard 12-lead electrocardiogram and stress testing as performed using our standard protocol.¹² Routine laboratory tests, chest roentgenogram and echocardiography were normal. Group B comprised 48 age- and gender-matched patients aged 40 to

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TABLE 1 Heart Rate and Blood Pressure Changes During Isometric Exercise

	Group A			Group B		
	Rest	Exercise	p Value	Rest	Exercise	p Value
Heart rate (beats/min)	62 ± 7	86 ± 7	<0.01	65 ± 6	91 ± 6	<0.01
Systolic blood pressure (mm Hg)	124 ± 8	152 ± 10	<0.001	131 ± 10	150 ± 8	<0.001
Diastolic blood pressure (mm Hg)	80 ± 5	89 ± 5	<0.05	84 ± 6	94 ± 8	<0.05
Mean arterial pressure (mm Hg)	95 ± 9	110 ± 9	<0.01	100 ± 7	112 ± 8	<0.01

Values are mean ± 1 standard deviation.

54 years (mean 49 ± 4) with preserved left ventricular function (ejection fraction $>55\%$) and proven CAD documented by a myocardial infarction ≥ 6 months before the study. The infarction was diaphragmatic in 13, high lateral in 7, anterior and diaphragmatic in 10 and anteroseptal in 18. All patients were in sinus rhythm and none had valvular or congenital heart disease, congestive heart failure or unstable anginal syndrome. No patient smoked. All medications were withdrawn ≥ 48 hours before testing, and subjects were instructed to refrain from eating and drinking coffee or tea ≥ 4 hours before the examination.

Exercise protocol: Isometric exercise was performed in the supine position using a standard 2-hand bar dynamometer. This device is a telescopic bar designed to be stretched simultaneously by both hands, determining the force of the voluntary isometric contraction in kilograms on a linear scale. The patients were instructed to exert the maximal compressive force on 3 occasions, with an interval of 3 minutes' rest between each. Maximal voluntary contraction was defined as the highest of the 3 attempts. After 10 minutes, subjects were required to perform 50% of their maximal voluntary contraction for 2 minutes. Echo-Doppler examination was performed at rest and at peak of exercise.

Aortic flow was recorded at held end-expiration. The subjects were instructed to avoid the Valsalva maneuver. Measurements were obtained from frozen images; 5 beats were averaged for each examination. Cuff sphygmomanometric blood pressure over the brachial artery was recorded at rest and before cessation of exercise. Mean arterial blood pressure was defined as (systolic pressure + diastolic pressure $\times 2$)/3. Heart rate was derived from the continuously registered electrocardiogram.

Doppler technique and measurements: Examinations were performed with a wide angle phased-array Hewlett Packard Sonos 500 imaging system using a pulsed Doppler transducer. Doppler studies were performed from the suprasternal notch, interrogating the ascending aorta. The sample volume depth was gradually adjusted until the optimal flow pattern was found, showing the highest velocity with the least spectral dispersion. Sample depth and position in the vessel remained constant throughout the study.

Peak flow velocity, expressed in cm/s, was defined as the midpoint of the upper portion of the Doppler signal at the time of maximal velocity. Ejection time, expressed in ms, was defined from the onset until the end of systolic flow; both points were determined by the time at which the Doppler signal crossed the 0-flow line. Acceleration time was defined as the time from onset of flow to the peak velocity and expressed in ms.

From these measurements, the following parameters were derived: Ejection time index was calculated by multiplying heart rate by 0.0016, adding the product to the measured ejection time¹³ and expressing the result in ms. Mean acceleration was calculated as peak velocity/acceleration time and expressed in m/s/s. The flow velocity integral, expressed in cm, was internally derived by the system on the basis of planimetric integration of the pixels included in the signal envelope.

Body surface area was determined from a Dubois nomogram. Stroke volume index was calculated as (flow velocity integral \times aortic orifice area)/body surface area, and expressed in ml/m². Stroke work was calculated as the product of stroke volume and mean arterial pressure, expressed in mW. Cardiac index was calculated as (flow velocity integral \times aortic orifice area \times heart rate)/body surface area, and expressed in liters/min/m².

Doppler examinations were registered at a speed of 100 mm/s and taped on a videotape recorder Panasonic AG-6200; the images were reviewed independently by 2 observers who were unaware of subjects' clinical data.

Two-dimensional echocardiographic measurements: With use of a 2.5-MHz phased-array transducer, parasternal short-axis left ventricular views were obtained from the third or fourth left intercostal space, and an apical 4-chamber view was obtained with the transducer in apical position.

The examinations were taped and the system was configured to produce a quad screen format. The video tape was reviewed in order to identify a single high-quality cycle; once identified, an electrocardiogram-triggered mechanism was automatically activated and the cycle was saved in the memory. Rest and exercise short-axis and apical 4-chamber views — 64 frames each — were displayed in the quad screen and com-

TABLE II Doppler Direct and Derived Measurements at Rest and During Isometric Exercise

Direct Measurements	Group A			Group B		
	Rest	Exercise	p (intragroup) Values	Rest	Exercise	p (intragroup) Values
Peak flow velocity (cm/s)	108 ± 13	79 ± 9	<0.001	98 ± 13	55 ± 12*	<0.001
Ejection time (ms)	292 ± 20	298 ± 18	NS	288 ± 17	299 ± 19	NS
Acceleration time (ms)	86 ± 7	99 ± 9	<0.05	82 ± 6	116 ± 7†	<0.01
Derived measurements						
Flow velocity integral (cm)	15 ± 3	11 ± 2	<0.05	14 ± 3	7 ± 3‡	<0.001
Ejection time index (ms)	393 ± 25	432 ± 28	<0.02	392 ± 33	440 ± 33	<0.02
Mean acceleration (m/s/s)	13 ± 1.4	8.8 ± 1	<0.01	11 ± 0.9†	4.7 ± 1‡	<0.001
Stroke volume index (ml/m ²)	46 ± 6	35 ± 5	<0.01	41 ± 6	23 ± 4‡	<0.001
Cardiac index (liters/min/m ²)	2.8 ± 0.3	3.0 ± 0.4	NS	2.7 ± 0.4	2.0 ± 0.2‡	<0.05
Stroke work (mW)	61 ± 3	67 ± 4	<0.05	56 ± 6†	57 ± 5†	NS

Values are mean values ± 1 standard deviation.
 Parentheses indicate intergroup significance: *p < 0.01; †p < 0.05; ‡p < 0.001.
 NS = not significant.

pared side by side as a continuous loop at various playback speeds. Left ventricular volumes (V) were determined as $V = 5/6 AL$, where A = short-axis area and L = left ventricular length.¹⁴ Detailed data on echocardiographic left ventricular volume and ejection fraction calculations are given in a previous report from our laboratory.¹⁵ The cross-sectional area of the aortic orifice was obtained from a standard parasternal long-axis view using the formula $\pi(\text{orifice diameter}/2)^2$.

Coronary angiography: Coronary angiography using a percutaneous transfemoral approach was performed with multiple views of each vessel in 44 subjects in group B (92%). Significant CAD was considered present when >75% stenosis of the luminal diameter was found in at least 1 major vessel.

Statistical analysis: Values are expressed as mean ± standard deviation. The percent change in Doppler-derived parameters of aortic flow during exercise was calculated as $[(\text{exercise value} - \text{rest value})/(\text{rest value})] \times 100$.⁴

Rest and exercise data within the groups were compared using Student's 2-tailed *t* test for paired observations and analysis between groups was conducted using the unpaired *t* test; *p* < 0.05 was considered significant.

RESULTS

Heart rate, blood pressure and electrocardiogram:

Heart rate and blood pressure changes during isometric exercise are summarized in Table I. There were no significant intergroup differences at rest and exercise. Exercise resulted in a significant increase in heart rate in both groups (*p* < 0.01). Systolic, diastolic and mean arterial pressure increased significantly (*p* < 0.001, *p* < 0.05 and *p* < 0.01, respectively) during exercise in both groups and the values returned to rest levels immediately on cessation of exercise. No patients presented with angina, and no ST-T changes or rhythm disturbances were documented.

Doppler direct measurements: Mean values for peak flow velocity, ejection time and acceleration time are listed in Table II. Peak flow velocity decreased during isometric exercise by a mean of 26% below rest levels in group A and a mean of 43% in group B (*p* < 0.001 for both; Figure 1). In both groups, ejection

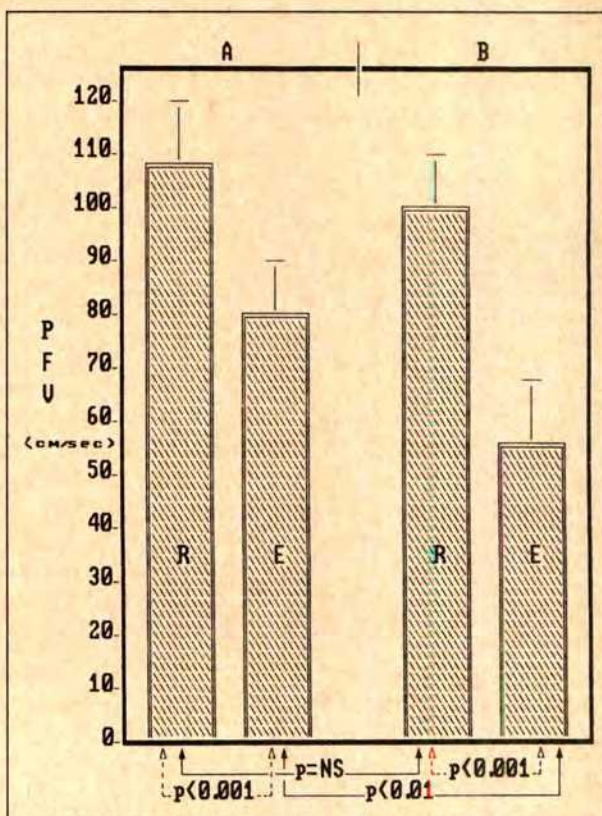


FIGURE 1. Peak flow velocity (PVF) in healthy controls (A) and patients with coronary artery disease (B) at rest (R) and during heavy isometric exercise (E). No significant differences were found at rest. At exercise, a significant reduction in peak flow velocity is documented in both groups, which was most marked in patients with coronary artery disease. The intergroup difference during exercise also was significant. NS = not significant.

TABLE III Exercise-Induced Changes in Peak Flow Velocity, Mean Acceleration, Left Ventricular Volumes and Ejection Fraction in Patients with Coronary Artery Disease

No. of Coronary Arteries Severely Narrowed	1		2		3	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
Peak flow velocity (cm/s)	103 ± 9	70 ± 5*	95 ± 8	61 ± 6*	96 ± 11	48 ± 7*
Mean acceleration (m/s/sc)	11.3 ± 0.8	6 ± 0.5*	11.1 ± 0.8	5 ± 0.5*	10.6 ± 0.8	4.2 ± 0.7*
End-systolic volume (ml)	33 ± 7	40 ± 6†	34 ± 8	43 ± 7†	34 ± 5	41 ± 7†
End-diastolic volume (ml)	91 ± 9	104 ± 9†	89 ± 7	106 ± 7†	92 ± 6	106 ± 8†
Ejection fraction (%)	63 ± 5	58 ± 7‡	64 ± 6	58 ± 6‡	61 ± 5	56 ± 5‡

*p < 0.0001; †p < 0.02; ‡p < 0.05, compared with values at rest. Values are mean ± 1 standard deviation.

time did not vary significantly with exercise. Acceleration time increased 16% in group A ($p < 0.05$) and 32% in group B ($p < 0.01$). No significant differences were found in any of the 3 parameters between the groups at rest. However, intergroup analysis of the results obtained on exercise showed a significant difference in peak flow velocity ($p < 0.01$) and acceleration time ($p < 0.05$) but not in ejection time.

Doppler-derived measurements: Mean values for Doppler-derived parameters are listed in Table II. Flow velocity integral and mean acceleration decreased during isometric exercise in both groups. In group A the mean reduction was 27% for flow velocity integral

($p < 0.05$ compared with rest value) and 33% for mean acceleration ($p < 0.01$); in group B the mean reductions were 50 and 57%, respectively ($p < 0.001$ for both). Ejection time index increased 10% in group A and 13% in group B ($p < 0.02$ for both). Stroke volume index decreased 22% in group A ($p < 0.01$) and 46% in group B ($p < 0.001$); cardiac index did not vary significantly in group A and decreased by 35% in group B ($p < 0.05$). Intergroup analysis did not show significant differences at rest for ejection time index, flow velocity integral, stroke volume index and cardiac output, but mean acceleration was significantly lower in group B ($p < 0.05$; Figure 2). During exercise, there were no significant differences between the 2 groups in terms of ejection time index. However, significantly lower values for flow velocity integral, mean acceleration, and stroke volume and cardiac indexes ($p < 0.001$ for all) were recorded in group B.

Rest and exercise stroke work values were lower in group B ($p < 0.05$); the values increased with exercise in group A ($p < 0.05$) and did not change significantly in group B.

Left ventricular volumes and ejection fraction: At rest, there was no significant difference between groups A and B in end-systolic (29 ± 4 and 33 ± 6 ml, respectively) and end-diastolic (91 ± 8 and 89 ± 9 ml, respectively) volumes. During exercise, end-diastolic volume was 94 ± 12 ml in group A ($p =$ not significant [NS]) and 106 ± 6 ml in group B ($p < 0.02$). End-systolic volumes changed to 34 ± 5 ml in group A ($p =$ NS) and to 42 ± 4 ml in group B ($p < 0.02$). Ejection fraction varied from 68 ± 7 to $65 \pm 8\%$ during exercise in group A ($p =$ NS) and from 63 ± 6 to $57 \pm 6\%$ in group B ($p < 0.05$). Intergroup comparison showed lower values in group B at rest ($p < 0.05$) and during exercise ($p < 0.02$). Mean values for the subgroups with 1-, 2- and 3-vessel disease are listed in Table III; no significant differences at rest or exercise were documented between the subgroups.

Analysis of the relation between exercise-induced Doppler patterns and coronary angiography: Of the 44 patients in group B who had undergone coronary angiography, 1-vessel disease was found in 15, 2-vessel dis-

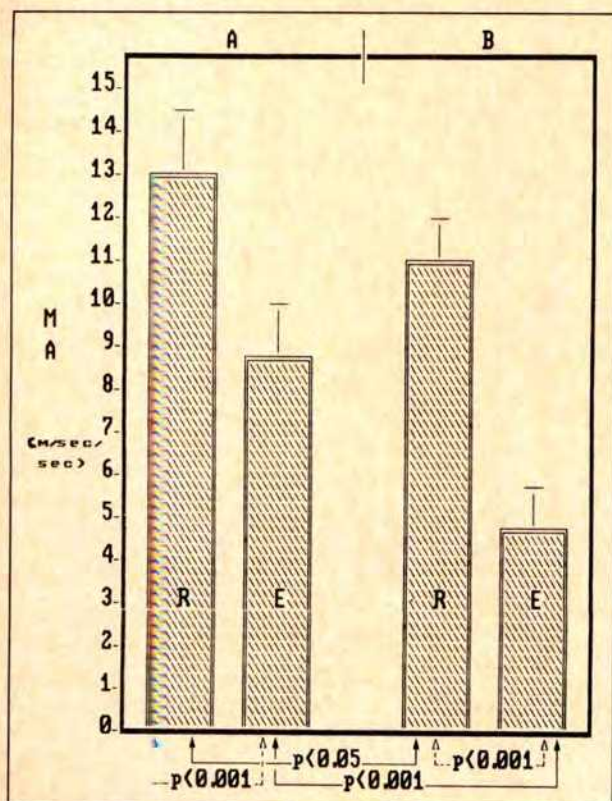


FIGURE 2. Mean acceleration (MA) in healthy controls (A) and patients with coronary artery disease (B) at rest (R) and during heavy isometric exercise (E). During exercise, significant reductions were documented in both groups. Rest and exercise values were significantly lower in patients with coronary artery disease.

ease in 16, and 3-vessel disease in 13. On the basis of the responses to exercise of the Doppler parameters, 3 patterns of response were noted. A type I response was defined as a decrease in peak flow velocity at exercise up to 65 cm/s (33%) and a decrease in mean acceleration up to 5.5 m/s/s (50%). A type II response was a decrease either of peak flow velocity to values <65 cm/s or of mean acceleration to values <5.5 m/s/s. A type III response was a decrease in both peak flow velocity and mean acceleration to lower values than those mentioned before. A type I response was seen in 12 subjects, all of whom had 1-vessel CAD (sensitivity 80%). A type II response was noted in 19 patients, 16 of whom had 2-vessel and 3 1-vessel CAD (sensitivity 84%). All the 13 patients with a type III response had 3-vessel disease (sensitivity 100%). The type III response had a specificity of 79% and a positive predictive value of 83%. Mean values of velocity and acceleration for these subgroups are given in Table III and individual delta values are depicted in Figures 3 and 4. The decreases of peak flow velocity and mean acceleration were 31 and 44%, 36 and 45%, 50 and 61%, respectively, in patients with 1-, 2- and 3-vessel CAD.

A weaker correspondence was found plotting the subgroups with 1-, 2- and 3-vessel disease against flow velocity integral, and stroke volume and cardiac index-

es, and no correspondence was found when plotting these subgroups against the responses to exercise of the remaining Doppler-derived parameters, left ventricular volumes or ejection fraction.

Variability and reproducibility: Rest and exercise Doppler images of satisfactory quality were obtained in all subjects. The differences between measurements by the same observer were 2.2% for ejection time, 3.1% for acceleration time and 3.2% for peak flow velocity. The differences between observers were 2.5, 2.9 and 3.4%, respectively. None of the differences were significant. To check the reproducibility, a second examination was performed the same day in 24 subjects (13 in group A and 11 in group B); no significant differences were detected for any of the parameters compared with the first examination. Correlation coefficient ranged from $r = 0.939$ to $r = 0.968$.

DISCUSSION

The influence of heavy isometric exercise on Doppler-derived parameters of aortic flow has not been examined. The main finding of the present study is that this type of exercise leads to marked changes in aortic

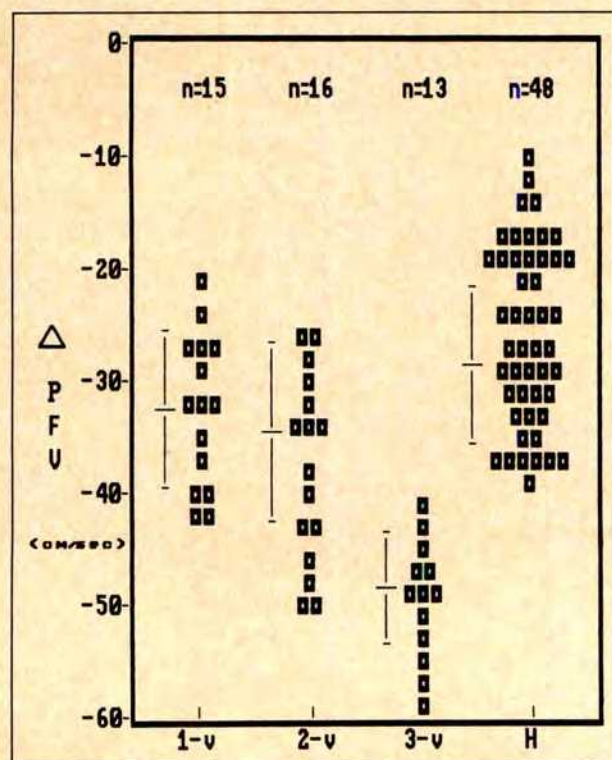


FIGURE 3. Individual peak flow velocity (PVF) reductions from rest to heavy isometric exercise in patients with 1-, 2- and 3-vessel (v) disease and in healthy control subjects (H). Mean delta values were -33 ± 5 (p = not significant compared with control values), -35 ± 8 ($p < 0.05$) and -48 ± 5 ($p < 0.001$), respectively; and -28 ± 7 in control subjects.

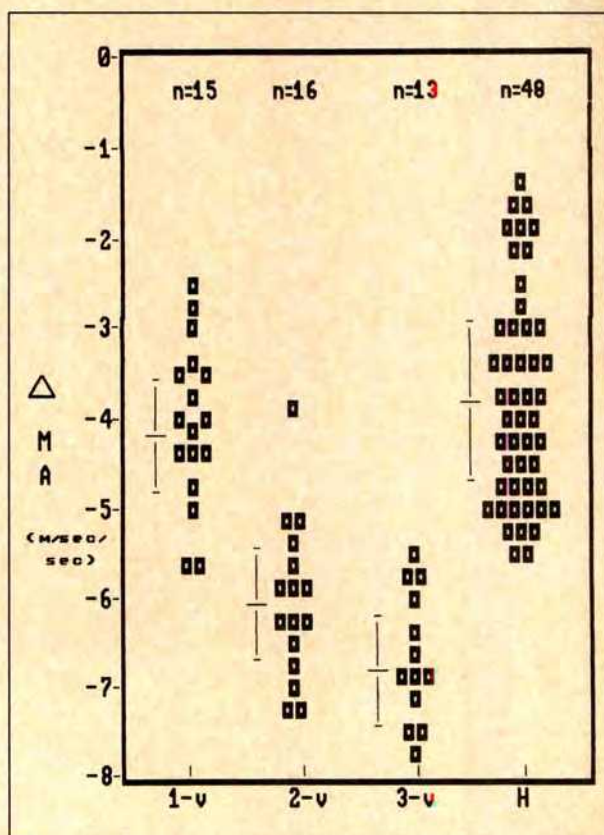


FIGURE 4. Individual mean acceleration (ΔMA) reduction from rest to heavy isometric exercise in patients with 1-, 2- and 3-vessel (v) disease and in healthy control subjects (H). Mean delta values were -4.1 ± 0.6 (p = not significant compared with control values), -6.1 ± 0.7 and -6.8 ± 0.5 ($p < 0.001$ for both), respectively; and -3.7 ± 0.8 in the control subjects.

flow patterns in normal subjects, and even more pronounced ones in patients with CAD.

Hemodynamic changes during isometric exercise:

The physiologic responses to isometric exercise in our patients were in many aspects similar to those seen in the control group. Heart rate, systolic, diastolic and mean arterial pressure and ejection time index increased, while ejection time did not change. Stroke volume index decreased in both groups. In group A the cardiac index increased as a result of the tachycardia, whereas in group B the tachycardia could not compensate for the abrupt reduction in stroke volume index, and the cardiac index decreased. Similar findings were recently reported by Keren et al¹⁶ in patients with congestive heart failure while performing isometric exercise. Stroke work in the control group increased during exercise, as previously reported,¹⁷⁻¹⁹ which would indicate a shift to a higher contractile state. In contrast, stroke work did not change in patients with CAD; this could be the result of a borderline-depressed contractility, which was unmasked by the pressure load imposed on the left ventricle during exercise. This loading also led to an increase in end-systolic volume and a decrease in ejection fraction that were not seen in the control subjects.

Pathophysiologic rationale of the method: Early animal studies, in which cardiac inotropism and blood flow dynamics were assessed with an electromagnetic flowmeter, showed that the acceleration of blood ejected from the left ventricle during early systole was an excellent indicator of the contractile state.²⁰ Subsequent human studies in which a catheter probe was used for evaluation of blood flow in patients with CAD found positive correlation between peak acceleration and ejection fraction.²¹ More recent studies using either continuous or pulsed Doppler echocardiography confirmed that measurement of aortic blood velocity and its derivatives is an accurate way to assess cardiac output and left ventricular function.^{1-3,22-26} We chose to measure mean rather than maximal acceleration because it is more readily and simply determined.¹⁷

Peak flow velocity increases during dynamic exercise^{4,5,7,22} and vasodilatation²⁷ and decreases during acute myocardial infarction²⁵ and during therapy with β blockade²⁸; these changes correlate with the different degrees of left ventricular function. Acceleration also increases during dynamic exercise²² and is very sensitive to changes of ventricular contractility, but is not influenced by preload. In experimental myocardial ischemia the acceleration decreases before any other changes and it has been considered the most sensitive index of inotropism.²⁰ This decrease has also been documented in clinical studies²⁵ with which our results are

in keeping. Our mean values for velocity and acceleration in healthy subjects are lower than those reported by Bryg et al¹⁷; this is probably due to the fact that our patients were older. However, the trend to reduction in the values of both parameters during isometric exercise was the same.

Study implications: The mean rest values for velocity and acceleration in patients with CAD were not significantly different from those for the control group. During exercise, the 2 parameters presented the same directional changes, complementing each other in suggesting the extent of CAD. The type III response was characterized by a pronounced reduction in both velocity and acceleration — 50% and about 60%, respectively — and all patients who presented with this response had 3-vessel disease. Most patients who showed a slight or an intermediate reduction had 1- and 2-vessel disease, corresponding to type I and type II responses, respectively. There was no significant difference in terms of flow velocity integral, and stroke volume and cardiac indexes between patients with CAD and healthy control subjects at rest, but the response to exercise allowed for a clear differentiation between groups. However, these responses did not discriminate between patients with 1-, 2- and 3-vessel disease.

Our study demonstrates that heavy isometric exercise results in significant reductions in peak flow velocity, and mean acceleration and flow velocity integrals in both healthy controls and patients with CAD. The exercise-induced changes in peak flow velocity and mean acceleration best separated normal persons from patients with CAD, and the degree of reduction in these values was directly related to the extent of CAD.

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Usefulness of Excitable Gap and Pattern of Resetting in Atrial Flutter for Determining Reentry Circuit Location

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Clinical and experimental data show that type I atrial flutter is due to a reentry mechanism with an excitable gap. To define the location of the reentry circuit of atrial flutter, width of excitable gap, poststimulation cycle and pattern of reset after premature stimulus were analyzed in 18 patients during atrial flutter at multiple atrial sites (high, lateral, posterior and septal right atrium, and coronary sinus). The pattern of reset was defined as flat or increasing whether the return cycle remained unchanged or prolonged with increasing prematurity. Shorter values of the excitable gap were found at the coronary sinus (33 ± 8 ms) and high right atrium (30 ± 10 ms) than at the posterior (43 ± 9 ms) or septal right atrium (45 ± 11 ms). Intermediate values (36 ± 8 ms) were measured at the lateral right atrium. Poststimulation cycle, corrected for atrial flutter cycle length, was shorter in the posterior (6 ± 7 ms) and septal right atrium (5 ± 7 ms) than in the coronary sinus (35 ± 9 ms), and the high (23 ± 10 ms) and lateral right atrium (15 ± 9 ms). A flat pattern of resetting occurred more frequently at the septal (18 of 18 patients) and posterior right atrium (15 of 18) than at the lateral (8 of 18) and high right atrium (2 of 17), and was never observed at the coronary sinus.

Atrial flutter was successfully terminated by overdrive atrial pacing in 15 of 18 patients, and termination was more easily obtained from the septal and posterior right atrium. The relation between shortest poststimulation cycle, flat pattern of resetting and widest excitable gap, probably identifies sites closer to the reentry circuit. This pattern is consistently observed at the sep-

tal and posterior right atrium. These criteria might be useful to improve efficacy in the electric termination of atrial flutter and in ablative therapy.

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Electrophysiologic studies of human atrial flutter indicate that this arrhythmia is due to a reentry mechanism.¹⁻³ The most frequent type of atrial flutter is due to circus movement in an anatomically defined pathway with a gap of full excitability.⁴ Interruption of this circus movement is the goal of many strategies that in recent years have been developed for the treatment of this arrhythmia. Termination of atrial flutter is best achieved by overdrive pacing,⁵⁻⁸ either alone or in combination with class IA antiarrhythmic drugs.⁹⁻¹¹ Overdrive termination of atrial flutter by means of implantable antitachycardia devices has been suggested as a suitable alternative to antiarrhythmic drug treatment for the long-term management of this arrhythmia.¹² Surgical division of the reentry circuit in the right atrium has been described to prevent recurrences of atrial flutter,² and the curative effect of transvenous endocardial ablation in recurrent atrial flutter¹³⁻¹⁵ has been demonstrated by several clinical studies. Localization of a crucial part of the reentry circuit is needed when any of these therapeutic interventions is considered. Programmed electrical stimulation during atrial flutter has been used to study the response of the arrhythmia to a single premature beat. The type of response has been used to define the chamber of origin of the arrhythmia,¹⁶ to prove the existence of a gap of full excitability,⁴ and to evaluate its size in relation to the cycle length of the arrhythmia^{4,17} and its changes induced by antiarrhythmic drug administration.¹⁸ The purpose of the present study was to investigate whether the type of resetting response to a single extrastimulus, the length of poststimulation cycle and the measure of excitable gap can be used to localize sites with easy access for permanent ablation of atrial flutter.

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METHODS

Study population: Eighteen patients (mean age 61 years) with long-lasting type I¹⁹ atrial flutter entered the study. In all 18 patients, the typical "sawtooth" pattern with negative F waves in leads II, III and aVF was documented. The mean cycle length was 229 ± 24 ms. No patient was taking antiarrhythmic drugs or other cardioactive medications at the time of the study.

Study protocol: Four quadripolar electrode catheters (interelectrode distance 0.5 cm) were percutaneously introduced in the femoral vein and placed at the following atrial sites: high and medium lateral right atrium (the same catheter was used for these 2 sites), inferior septum, posterior right atrium and coronary sinus. Simultaneous bipolar recording and pacing could be performed at each of the aforementioned sites. Single atrial extrastimuli (pulse duration 2 ms and intensity 10 mA) were delivered at each site. The entire atrial flutter cycle was scanned at 10-ms decrements until local refractoriness was encountered. Stimulation was performed using a Medtronic programmable stimulator (model SPO503). Simultaneous recordings of 6 surface electrocardiographic leads (I, II, III, aVR, V₁ and V₆) and bipolar intracavitary electrograms from the standard atrial sites were performed on a multichannel Siemens T16 recorder at a paper speed of 100 mm/s.

After this procedure was completed at all standard sites, overdrive pacing was attempted for termination of the arrhythmia. Stimulation at an intensity of 10 mA was initiated, starting at 1 of the aforementioned sites selected according to a randomized scheme, with a cycle length 10 ms less than the atrial flutter cycle length for 1 minute. If reversion to sinus rhythm did not occur, the pacing cycle was shortened by 10-ms steps and the procedure was repeated until sinus rhythm was recovered or attained a minimum-paced cycle of 150 ms. The same procedure was repeated at different atrial sites until recovery of sinus rhythm or induction of atrial fibrillation.

Definitions: In all patients, the following parameters were evaluated at each recording site:

CAPTURE ZONE: This zone was the difference between the longest coupling interval causing local capture and the shortest extrastimulus causing a resetting response.

EXCITABLE GAP (RESET ZONE): This reset zone was the difference between the longest and shortest extrastimuli causing a resetting response. Resetting was defined by (1) occurrence of a less than compensatory pause after the extrastimulus as measured at the stimulation site leading to ≥ 20 -ms advancement of the atrial cycle, and (2) resumption of atrial flutter with the same surface electrocardiographic morphology and intracavitary activation pattern. The coupling interval was measured as

the distance between the fast deflection of the stimulated electrogram.

POSTSTIMULATION CYCLE: This was the cycle following the atrial extrastimulus. This was measured at the stimulation site after the longest coupling interval causing reset. Poststimulation cycle was corrected in all cases by subtracting atrial flutter cycle length.

PATTERN OF RESETTING: This pattern was defined as either flat or increasing depending on whether poststimulation cycle was constant or increased with increasing prematurity.

Statistical analysis: The Shaffer extension of Dunnett's test, a nonparametric procedure allowing multiple comparisons, was used.²⁰ Specifically, the extension of Friedman type for all variables was applied. The statistical analysis of pattern of resetting response, being a dichotomic variable, was performed by the extension of Cochran type.

RESULTS

The mean cycle length of atrial flutter was 229 ± 24 ms (Table I). In all patients the arrhythmia remained stable throughout the study, thus allowing evaluation of the capture zone, excitable gap, poststimulation cycle and pattern of resetting at multiple atrial sites during the same episode of atrial flutter. Coronary sinus catheterization was achieved in 15 of 18 patients. The single extrastimulus did not cause acceleration into atypical atrial flutter or atrial fibrillation in any patient. In 1 patient (no. 2), a single extrastimulus reproducibly terminated the arrhythmia.

Capture zone and excitable gap: Values of the capture zone were similar at all sites, slightly longer values being observed at the distal coronary sinus and high right atrium than at the remaining right atrial sites. Values recorded at the posterior and septal right atrium were significantly shorter ($p < 0.01$) than those at the coronary sinus. The excitable gap could be evaluated at the coronary sinus in 12 of 15 patients and at the high right atrium in 17 of 18, because a reset response could not be elicited in 3 and in 1 patient, respectively. However, reset was always present at the other right atrial sites. The excitable gap was shorter at the coronary sinus and high right atrium (Figure 1); the excitable gap was significantly longer at the posterior (Figure 2) and septal right atrium ($p < 0.05$) than at the coronary sinus. Intermediate values were measured at the lateral right atrium. Among right atrial sites, although the excitable gap was longer at the posterior and septal right atrium, only comparisons between the septal and high right atrium ($p < 0.01$) and between the septal and lateral right atrium produced statistically significant results ($p < 0.05$).

TABLE I Electrophysiologic Variables in 18 Patients with Type I Atrial Flutter

Pt. No.	CL (ms)	Loc. ERP (ms)					Capture Zone (ms)					Excitable Gap (ms)					PSCL-CL (ms)					RRP (ms)				
		HRA	LRA	PRA	SRA	CS	HRA	LRA	PRA	SRA	CS	HRA	LRA	PRA	SRA	CS	HRA	LRA	PRA	SRA	CS	HRA	LRA	PRA	SRA	CS
1	240	15C	170	150	140	140	90	70	90	100	100	30	30	40	60	30	40	0	0	0	30	F	F	F	F	I
2	220	17C	150	160	170	150	50	70	60	50	70	20	30	40	20	40	10	20	0	0	50	I	F	F	F	I
3	280	14C	140	170	160	130	140	140	110	120	150	50	50	60	60	50	40	30	20	0	40	I	F	F	F	I
4	260	13C	150	180	170	—	130	110	80	90	—	50	50	50	50	—	30	20	0	0	—	I	I	F	F	—
5	210	15C	150	150	160	130	60	60	60	50	80	30	30	30	40	30	20	20	10	0	40	F	I	F	F	I
6	240	15C	140	150	160	140	90	100	90	80	100	40	40	50	50	30	10	20	10	0	20	I	I	I	F	I
7	220	15C	140	160	160	140	70	80	60	60	80	30	40	40	40	40	20	10	10	10	20	I	F	F	F	I
8	260	14C	170	160	180	150	120	90	100	80	110	40	40	40	50	—	20	20	10	0	—	I	I	I	F	—
9	200	13C	150	150	150	—	70	50	50	50	—	20	20	30	30	—	30	10	0	0	—	I	F	F	F	—
10	240	18C	150	140	140	130	60	90	100	100	110	20	30	50	50	40	0	10	10	10	30	I	F	F	F	I
11	200	13C	130	120	140	130	70	70	80	60	70	30	30	50	30	20	20	10	0	0	40	I	I	F	F	I
12	230	13C	140	150	150	130	100	90	80	80	100	30	40	30	50	30	30	0	0	20	40	I	I	I	F	I
13	220	14C	140	140	140	140	80	80	80	80	80	20	30	50	50	30	30	10	20	20	30	I	F	F	F	I
14	260	16C	160	180	140	140	100	100	80	120	—	—	40	50	50	—	—	10	0	0	—	I	F	F	F	—
15	200	14C	140	150	140	—	60	60	50	60	—	20	30	30	40	—	30	30	0	0	—	I	I	F	F	—
16	200	13C	150	140	150	130	70	50	60	50	70	20	40	40	40	30	20	10	0	10	40	I	I	F	F	I
17	220	14C	150	150	150	135	80	70	70	70	90	40	40	40	40	30	20	30	0	0	40	I	I	F	F	I
18	230	14C	160	140	140	130	90	70	90	90	100	30	40	50	60	—	20	10	10	10	—	I	F	F	F	—
Mean	229	14C	149	152	152	135	85	80	77	77	94	30	36	43	45	33	23	15	6	5	35					
± SD	24	14	11	15	13	6	25	23	18	23	22	10	8	9	11	8	10	9	7	7	9					

CL = cycle length; CS = coronary sinus; ERP = effective refractory period; F = flat; HRA = high right atrium; I = increasing; LRA = lateral right atrium; PRA = posterior right atrium; PSCL = poststimulation cycle length; RRP = resetting response pattern; SRA = septal right atrium.

Poststimulation cycle and pattern of resetting: The poststimulation cycle, measured at the stimulation site and corrected for the atrial flutter cycle, was significantly shorter in the posterior and septal right atrium than in the coronary sinus ($p < 0.05$). The comparisons among right atrial sites revealed that the poststimulation site was significantly shorter in septal than in the

high ($p < 0.01$) and lateral right atrium ($p < 0.05$). As mentioned previously in Methods, these values refer to the cycle following the longest coupling interval with a reset response. When the coupling interval was progressively shortened, the poststimulation cycle remained similar until the refractory period in some patients (flat pattern), or showed either sudden or progressive in-

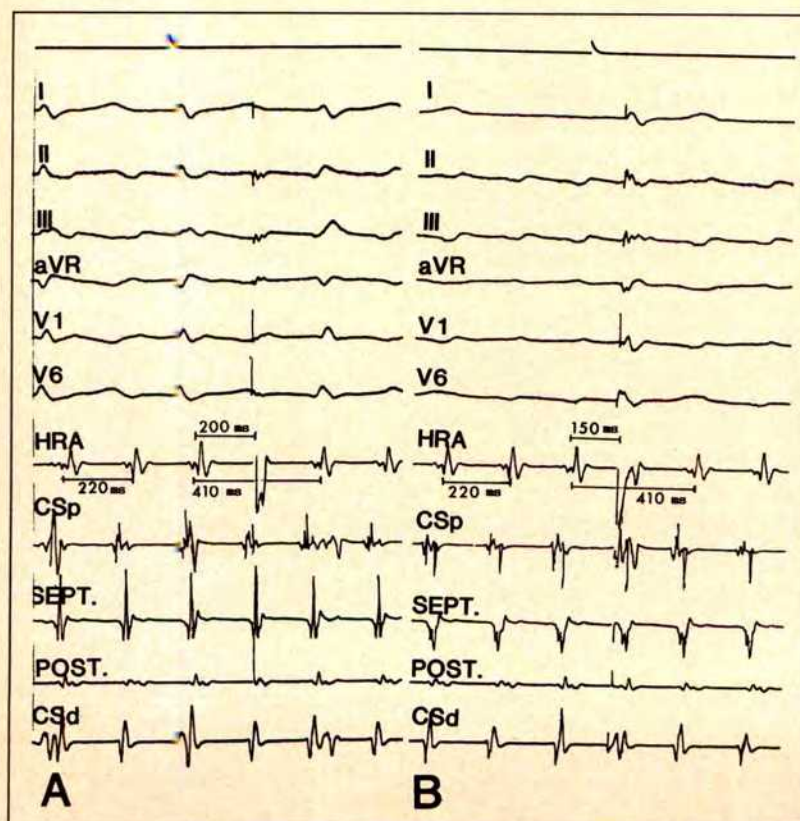


FIGURE 1. Simultaneous surface electrocardiographic leads and intracavitary recordings are shown. **A**, measurement of excitable gap at high right atrium. Reset can be observed following an extrastimulus with a prematurity of 200 ms. **B**, reset is observed at 150 ms with an increased return cycle. CSd = distal coronary sinus; CSp = proximal coronary sinus; HRA = high right atrium; POST. = posterior right atrium; SEPT. = septal right atrium.

creases in other patients (increasing pattern) (Figure 3). A flat pattern of resetting was observed more frequently in the septum (18 of 18 patients) and posterior right atrium (15 of 18) than in the lateral (8 of 18) and high right atrium (2 of 17). This pattern of response was never observed at the coronary sinus in the 12 patients in whom the resetting response could be elicited; in these patients the pattern of reset was always increasing. These differences were statistically significant. An increasing pattern of reset was observed in the remaining patients at the other atrial sites.

Termination of atrial flutter: role of the stimulation site (Table II): In 1 patient (no. 2) atrial flutter could be reproducibly terminated by 1 extrastimulus at the posterior right atrium; in this patient the arrhythmia could not be interrupted by a single extrastimulus delivered at the other atrial sites. In the remaining 17 patients, overdrive pacing was performed as described in Methods. Sinus rhythm could be recovered in 14 of 17 patients; in 3 patients atrial fibrillation was induced as a consequence of overdrive pacing. Successful termination of atrial flutter was achieved by pacing at the posterior

FIGURE 2. A, reset is obtained earlier at the posterior right atrium (210 ms). B, reset is observed at the prematurity of 160 ms. No prolongation of the return cycle is observed following this shorter coupled extrastimulus. Abbreviations as in Figure 1.

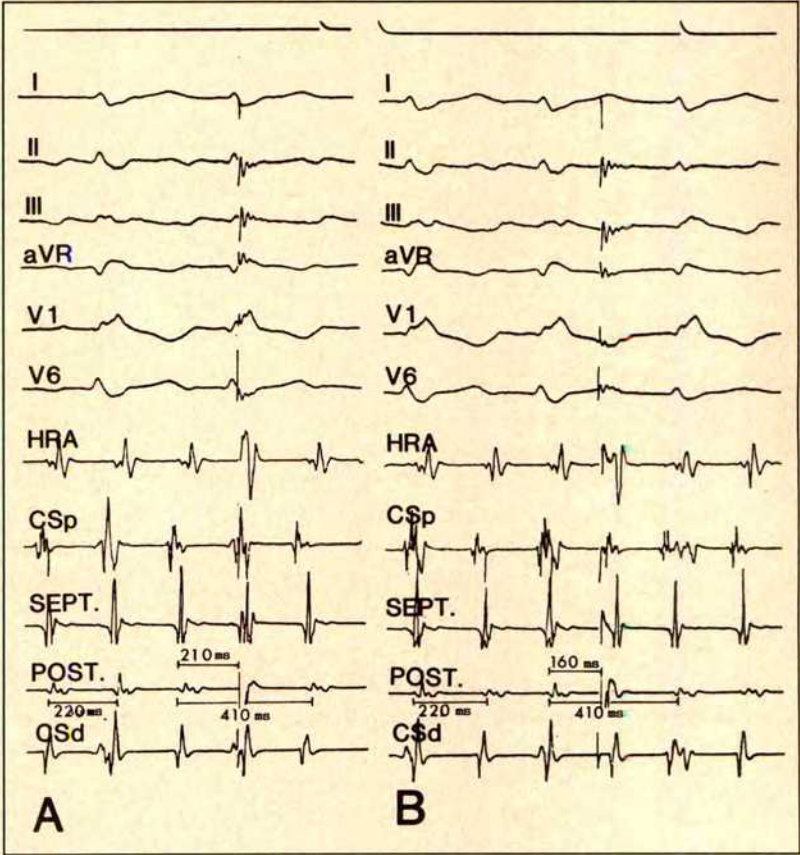


FIGURE 3. Evaluation of the pattern of resetting to a single extrastimulus at multiple atrial sites during atrial flutter (cycle length = 220 ms). A flat pattern of reset is observed at the posterior right atrium (POST.). Increasing pattern of reset are observed at the high (HRA) and septal right atriums (SRA) and coronary sinus (CS). Note that reset is obtained with longer coupling interval at POST. (210 ms) than at other atrial locations. Reset is initiated only at higher prematurities at the CS. A1-St = coupling interval of atrial extrastimulus; PSC = poststimulation cycle (measured at stimulation site).

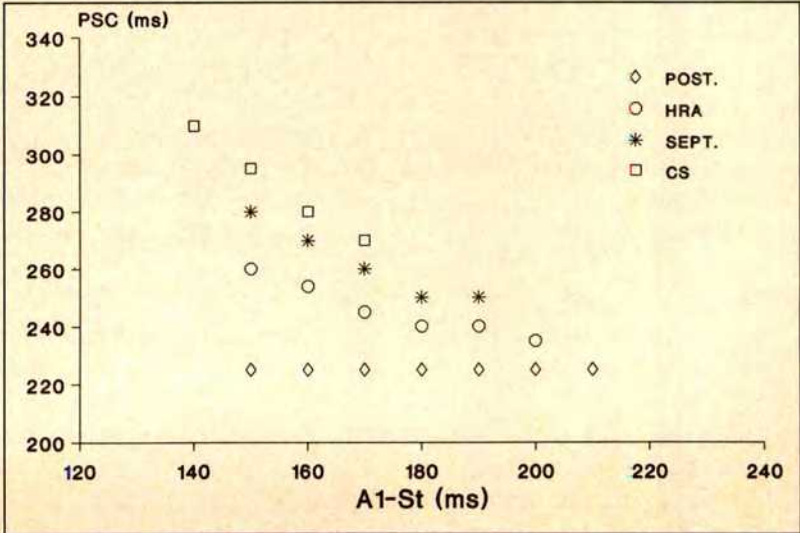


TABLE II Termination of Atrial Flutter by Overdrive Pacing: Results and Stimulation Sites

Pt. No.	Overdrive Pacing	Effective Site	I Stimulated Site	II Stimulated Site	III Stimulated Site
1	SR	LRA	CS	LRA	—
2	SR*	PRA	PRA	—	—
3	SR	SRA	LRA	SRA	—
4	SR	PRA	PRA	—	—
5	SR	SRA	HRA	SRA	—
6	Af	—	LRA	SRA	PRA
7	Af	—	HRA	—	—
8	SR	SRA	LRA	CS	SRA
9	SR	PRA	PRA	—	—
10	SR	PRA	CS	HRA	PRA
11	SR	SRA	SRA	—	—
12	SR	PRA	HRA	CS	PRA
13	SR	SRA	SRA	—	—
14	SR	PRA	PRA	—	—
15	SR	PRA	CS	PRA	—
16	SR	SRA	SRA	—	—
17	SR	SRA	SRA	—	—
18	Af	—	HRA	—	—

*By single extrastimulus; in this patient termination of atrial flutter by single extrastimulus was attempted, unsuccessfully, at all other atrial sites.
Af = atrial fibrillation; CS = coronary sinus; HRA = high right atrium; LRA = lateral right atrium; PRA = posterior right atrium; SR = sinus rhythm; SRA = septal right atrium.

right atrium in 7 patients (in 4 as a first-tested site, in 1 after failure at the coronary sinus and in 2 after failure at the high right atrium and coronary sinus), at the septal right atrium in 7 (in 4 as the first pacing site, in 2 as a second attempt and in 1 after failure at the lateral right atrium and coronary sinus), and at the lateral right atrium in 1 (as a first attempt). The electrophysiologic properties of the sites where atrial flutter was terminated are summarized in Table III. Table III shows that in 14 of 15 patients in which sinus rhythm was recovered, the pattern of reset was flat. Table III also shows that the values of poststimulation cycle and excitable gap were shortest at the sites where sinus rhythm was recovered than at the sites tested previously.

DISCUSSION

Single extrastimulus testing during atrial flutter has been used to demonstrate the reentry mechanism of the arrhythmia¹⁻³ and to identify the chamber of origin.¹⁷ In this study, the response to a single atrial extrastimulus, i.e., length of poststimulation cycle, pattern of reset and amplitude of excitable gap, was different at various atrial sites. We investigated the significance of this finding.

Capture zone and excitable gap: The duration of the capture zone was frequently wider than the excitable gap, because at many sites local capture could occur without advancement of the tachycardia cycle. This phenomenon, which has already been described by Watson and Josephson¹ in atrial flutter and by Lai et al²¹ in atrioventricular reciprocating tachycardia, oc-

TABLE III Electrophysiologic Properties of the Sites Where Atrial Flutter was Terminated

Pt. No.	Site	RRP (ms)	PSCL-CL (ms)	EG/MaxEG (ms)
1	LRA	F	0	30/60
2	PRA	F	0	40/40
3	SRA	F	0	60/60
4	PRA	F	0	50/50
5	SRA	F	0	40/40
6*	PRA	I	10	50/50
7*	HRA	I	20	30/40
8	SRA	F	0	50/50
9	PRA	F	0	30/30
10	PRA	F	10	50/50
11	SRA	F	0	30/50
12	PRA	I	0	30/50
13	SRA	F	20	50/50
14	PRA	F	0	50/50
15	PRA	F	0	30/40
16	SRA	F	10	40/40
17	SRA	F	0	40/40
18*	HRA	I	20	30/60

*Atrial fibrillation induced by overdrive pacing.
EG = excitable gap; MaxEG = maximal excitable gap; other abbreviations as in Table I.

curs at longer coupling intervals. The reset zone begins with coupling intervals that were shorter at the coronary sinus or high or lateral right atrium than at the septum or posterior wall of the right atrium. The excitable gap, therefore, is the widest measured at these latter sites. Underestimation of the tachycardia excitable gap, due to intervening tissue between the stimulation site and exit point of the reentry circuit, frequently occurs; therefore, probably the widest measurement represents the best approximation of the true excitable gap.

Pattern of resetting and poststimulation cycle: During the same episode of atrial flutter, the pattern of resetting was either flat or increasing at different stimulation sites. In all patients, however, a flat pattern of reset could be identified in at least 1 right atrial site, thus suggesting the presence of a fully excitable gap.²² The observation of an increasing pattern of reset during the same episode of arrhythmia probably reflects decremental conduction properties of atrial tissue between stimulation site and reentry circuit.²³ This is further supported by the finding of short return cycles at sites with a flat pattern of reset. The sites with a shorter return cycle were always characterized by a wider excitable gap; the pattern of reset was always flat at these sites, suggesting a fully excitable gap. These characteristics are likely to identify sites at closer proximity or with easier functional access to a crucial part of the reentry circuit, or both.

According to mapping studies, an area of slow conduction can be found in all patients with type I atrial flutter in the posteroinferior right atrial wall.¹⁴⁻¹⁶ A possible consequence of this finding could be an easier

termination of the arrhythmia when overdrive pacing is performed from these sites.

Clinical implications: Atrial flutter termination by overdrive pacing has a variable rate of success depending on many factors. The distance between stimulation site and reentry circuit may be responsible for failure in termination of the arrhythmia.²⁴ The results of this study indicate that atrial flutter is terminated more easily when overdrive pacing is performed from the posterior or posteroseptal right atrium. The electrophysiologic properties of the sites where arrhythmia was terminated are listed in Table III. The data show that in 14 of 15 patients a flat pattern of reset could be demonstrated at sites of arrhythmia termination and that in most patients the widest excitable gap and the shortest poststimulation were at these sites. Stimulation at coronary sinus was ineffective in all patients and sinus rhythm was recovered at the lateral right atrium in only 1 patient. Furthermore, in several patients, stimulation at the posterior or septal right atrium was successful after pacing had failed at other locations; stimulation at the posterior or septal right atrium was always effective. In their interesting mapping studies during atrial flutter, Cosio et al¹⁷ described a high prevalence of double-spike electrograms in the posterior wall of the right atrium and have suggested that they may identify a zone of slow conduction. Successful catheter ablation of atrial flutter has been described by Chauvin and Brechenmacher¹³ when direct-current shocks were applied to this area. More recently, Saoudi et al¹⁵ described successful atrial flutter ablation in a series of 8 patients. Direct-current shocks were delivered to a slow conduction area, identified in all patients by entrainment criteria, in the posterior right atrial wall.

The identification by single extrastimulus of sites having a flat pattern of reset, a wide excitable gap and a short poststimulation cycle may guide the choice of the site for transvenous endocardial ablation of atrial flutter.

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Effects of Exercise on Heart Rate, QT, QTc and QT/QS2 in the Romano-Ward Inherited Long QT Syndrome

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Patients with the Romano-Ward inherited long QT syndrome have an incompletely defined cardiac sympathetic system abnormality, and exhibit ventricular arrhythmias during exercise, fear and anxiety. Treadmill and bicycle exercise were used to modulate cardiac autonomic activity in 27 Romano-Ward subjects and 27 normal controls. The heart rate, and the QT, QTc and QT/QS2 (ratio of electrical to mechanical systole) intervals were compared. Subjects with long QT were compared with normals. Those with a long QT interval had the following results: similar resting heart rates; lower rates during moderate (151.6 vs 159.6 beats/min, $p = 0.04$) and maximal (155.9 vs 182.1 beats/min, $p < 0.001$) exercise; an abnormal QT cycle-length relationship, with failure of the QT to shorten normally with increasing heart rate; an increase in QTc versus a decrease in normals; supine rest QT/QS2 ratio of 1.12 vs 0.93, $p = 0.001$; and an exercise QT/QS2 that increased by 30%, from 1.12 at rest to 1.45, versus 15%, in normals, from 0.93 to 1.07, $p = 0.001$. The lower heart rates and excessively prolonged QT/QS2 ratios during exercise further support an abnormality of, or abnormal cardiac response to, sympathetic activity. A QT/QS2 > 1.0 at rest, an exercise QT/QS2 ratio > 1.17 , and an increase in QTc during moderate exercise may be helpful diagnostic findings in patients with borderline long QTc intervals at rest.

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The Jervell and Lange-Nielson,¹ Romano-Ward^{2,3} inherited long QT syndromes are characterized by exercise or stress-induced ventricular arrhythmias, syncope and sudden death. A number of studies have shown an incompletely defined abnormal relation with the cardiac sympathetic system.⁴⁻¹² The usual precipitation of the arrhythmias by exercise and sudden emotional stress, times at which sympathetic activity is enhanced, suggests that electrocardiographic or other measurements during exercise may be particularly helpful in the study of the pathophysiology of the syndromes. We therefore used exercise to enhance sympathetic activity and evaluated the heart rate, and QT, QTc and QT/QS2 intervals as measures of the effect of the sympathetic stimulation in patients with the Romano-Ward syndrome. Because the diagnosis is difficult in some patients with borderline QT prolongation, these measurements during exercise were also evaluated for diagnostic utility.

METHODS

The studies were performed in 27 subjects with Romano-Ward long QT chosen from a family with an 8-generation pedigree and autosomal dominant inheritance. None of the Romano-Ward subjects were taking β blockers or other medications. A remote history of palpitations, near syncope or syncope was present in 13 of 27 subjects antedating our diagnosis, and no medications were begun. In 2 of 15 subjects, including 1 with a history of cardiac arrest, remote syncope had occurred, and they had only "premonitory" symptoms during significant exercise. They had learned to avoid symptoms by stopping exercise before onset of such feelings. Both led normal lifestyles and were unwilling to take medication. These 2 were entered into the bicycle protocol because of the lesser exercise required. There were 27 normal subjects with no history of heart disease, normal physical examinations and electrocardiograms, and who took no medications. Symptom-limited maximal effort treadmill tests were used to evaluate the heart rate response to exercise. Bicycle tests were used to evaluate QT/QS2 response. QT and QTc response to exercise were evaluated with both forms of exercise. The QT and QS2 measurements were the average of 3 sequential beats. All measurements were made by a single ob-

server (GMV) with many years of experience in evaluating the Romano-Ward syndrome, to enhance consistency of QT measurements. The offset of the QT interval was taken as the point of maximal slope change as the downslope of the T wave merged with the baseline. The modest heart rates obtained during bicycle exercise did not produce T- and P-wave fusion, and exercise measurements were obtained as mentioned. Such fusion was present in several of the treadmill test tracings, and the end of the T wave was taken as the point where continuation of the line of most rapid descent transected the baseline. The QTc was calculated using Bazett's formula. All protocols were approved by the Institutional Review Board for Human Research. All study participants gave informed consent.

Heart rate evaluation: Twenty subjects with Romano-Ward syndrome (mean QTc 0.49 ± 0.02) and 20 normal volunteers (QTc 0.40 ± 0.02) were studied with maximal effort treadmill tests. An initial 12 subjects with Romano-Ward syndrome and controls (group I) were studied evaluating only maximal heart rate achieved. When a lower maximal rate was seen in the Romano-Ward subjects, a second group of 8 Romano-Ward subjects and 8 normals was studied to evaluate the heart rate response throughout exercise (group II). The 12-lead electrocardiogram and symptoms were monitored continuously. Heart rate and lead II QT interval were recorded at rest, at the end of each stage of exercise (group II) or at maximal exercise only (group I), and immediately, 1, 3 and 5 minutes after exercise. Predicted maximal heart rate was calculated for each subject using the formula $220 - \text{age}$.

GROUP I: This group consisted of 12 Romano-Ward subjects (QTc 0.49 ± 0.02 , mean age \pm standard deviation 17.1 ± 11.2 years) 8 men, and 12 sex- and age-matched controls (QTc 0.40 ± 0.02). A history of symptoms was present in 4 of 12 Romano-Ward patients.

GROUP II: In this group were 8 Romano-Ward subjects (QTc 0.48 ± 0.02 , aged 34.8 ± 9.5 years) 5 women, and 8 sex- and age-matched normal controls (QTc 0.40 ± 0.02). A history of symptoms was present in 4 of 8 Romano-Ward patients.

STATISTICAL ANALYSIS: Heart rate data are expressed as mean \pm standard deviation. Mean heart rates at maximal exercise in both group I and II subjects with long QT were compared with those of their respective control group, and with the age-predicted maximal rate, using Student's *t* test. Mean heart rates at each stage of exercise and recovery were compared in group II patients with Romano-Ward syndrome and in normals using analysis of variance. Statistical significance for all comparisons was <0.05 .

QT/QS2 interval: The QT/QS2 ratio is a comparison of electrical systole (QT interval) with mechanical

systole (QS2 interval); several studies have indicated that the QT/QS2 ratio reflects autonomic tone¹³⁻¹⁵ with a normal QT/QS2 ratio <1.0 at rest increasing to just >1.0 with exercise. The increase is due to the QS2 interval shortening slightly more during exercise than does the QT interval, and this differential effect on QS2 versus QT is thought to be the result of increased sympathetic activity.¹³⁻¹⁵

There were 7 Romano-Ward subjects, 3 women, aged 25.5 ± 9.2 years (range 20 to 43), with a QTc of 0.48 ± 0.04 . The 7 normals and 3 women were similar in age, 26.6 ± 9.5 years (range 20 to 40) (QTc 0.38 ± 0.03). All 7 Romano-Ward subjects had previous symptoms as previously noted. Prolonged QTc intervals had been noted in 2 subjects on previous electrocardiograms and QTcs of 0.44 and 0.45, respectively, were present on their baseline records. These 2 were specifically included in the study so that Romano-Ward subjects with a range of QTc intervals were represented. Modest bicycle exercise was chosen to avoid serious rhythm disturbances and to improve the quality of the QT and QT/QS2 measurements. The protocol consisted of 3-minute stages, beginning at a 25-W work load, increasing by 25 W each 3 minutes through 12 minutes. A 12-lead electrocardiogram for QT measurements, and a lead II and second left intercostal space phonocardiogram at 100 mm/s for the QT/QS2 interval, were recorded at rest, at the end of each stage of exercise, and at 1, 3, 5 and 8 minutes after exercise. The QS2 interval was measured from the onset of ventricular depolarization in lead II to the first high frequency deflection of the aortic component of the second heart sound.

STATISTICAL ANALYSIS: The data are expressed as mean \pm standard deviation (except in Figure 4 where the data are shown as mean \pm standard error for better graphic display). The QT, QTc and QT/QS2 intervals at each stage of exercise and recovery were compared with measurements at the rest stage in both Romano-Ward and control groups using analysis of variance to determine if significant changes occurred with exercise. Comparison between subjects with the Romano-Ward syndrome and controls at each stage of exercise and recovery was performed using Student's *t* test for unpaired observations.

RESULTS

Heart rate response: **GROUP I—MAXIMAL HEART RATE:** There was no difference in resting heart rates for Romano-Ward subjects versus controls (77 ± 10 vs 76 ± 10 beats/min). The time on the treadmill was similar at 9.8 minutes for Romano-Ward syndrome versus 10.5 minutes for controls ($p > 0.1$). The maximal rate achieved by subjects with Romano-Ward syndrome was 156 ± 10 beats/min, significantly lower

than those in normals (188 ± 9.2 beats/min), and the age-predicted maximum of 197 ± 9.5 beats/min ($p < 0.001$) for both comparisons. There was no significant difference between the rate of normals and the predicted rate.

GROUP II — HEART RATE RESPONSE THROUGHOUT EXERCISE: The heart rates at each stage of exercise and recovery for group II Romano-Ward subjects and normal controls are shown in Figure 1. The time on treadmill was similar at 9.1 ± 2.2 minutes for Romano-Ward

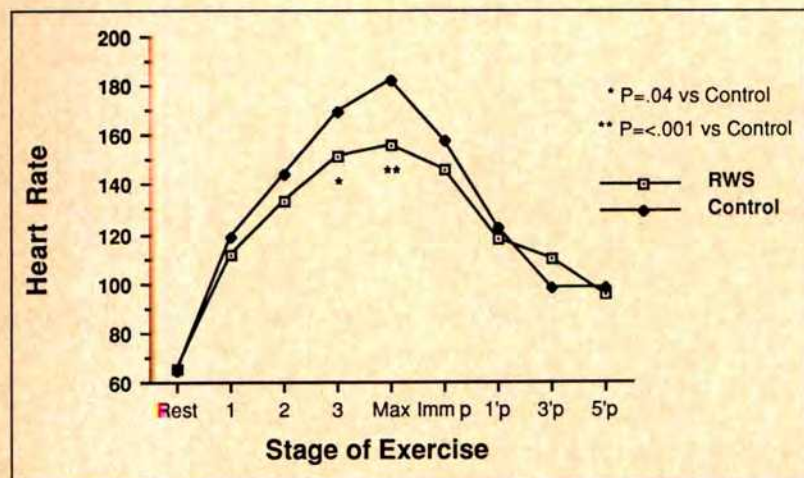


FIGURE 1. Heart rate during treadmill exercise. Mean heart rates in group II control subjects and subjects with Romano-Ward syndrome (RWS) during exercise and recovery. There was a significantly lower rate in subjects with RWS long QT interval at the end of stage 3 ($p = 0.04$) and at maximal exercise ($p < 0.001$) compared with values in normals. Imm = immediate recovery; Max = maximal exercise; 1'p, 3'p, 5'p = 1, 3 and 5 minutes after exercise, respectively.

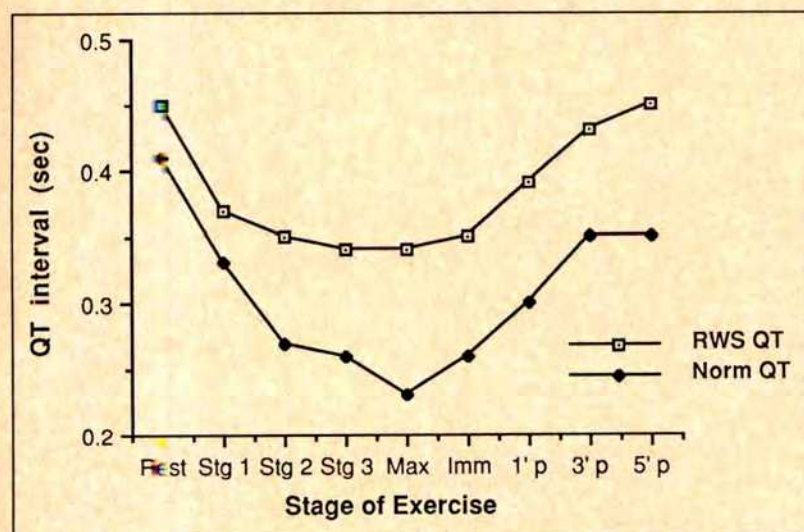


FIGURE 2. QT interval during treadmill exercise. A plot of the changes in QT interval at each stage (Stg) of exercise and recovery. An abnormal dynamic relation is seen in subjects with Romano-Ward syndrome (RWS). The QT of the subjects with RWS shortened through stage 1 at a rate similar to normals, but did not shorten further after stage 2 despite continued increments in heart rate; the QT of normals (Norm QT) shortened continuously throughout exercise. The RWS QT is significantly longer than in normals at each stage: $p = < 0.01$ at rest and stage 1; $p = < 0.001$ at all other times. Abbreviations as in Figure 1.

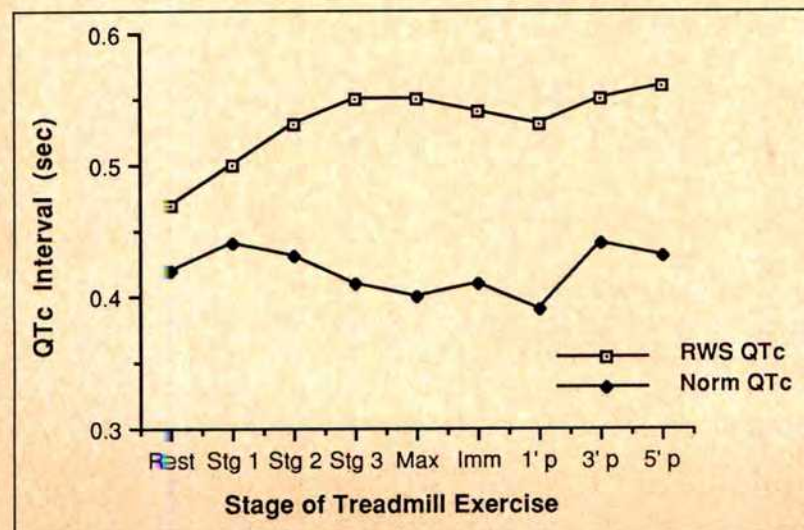


FIGURE 3. QTc response during treadmill exercise. The QTc of subjects with Romano-Ward syndrome (RWS) was significantly longer than in normals at rest and at each stage of exercise and recovery, $p < 0.01$ to < 0.001 . The QTc of normals (Norm QTc) showed no significant change during exercise compared with the rest value, whereas the subjects with RWS demonstrated a significant increase in QTc throughout exercise; $p < 0.002$ at stage 3 and maximal exercise compared with the rest value. Note a further lengthening of the QTc in subjects with RWS at 3 and 5 minutes of recovery. Abbreviations as in Figure 2.

subjects compared with 9.8 ± 2.0 minutes for controls ($p = 0.4$). The resting heart rates were similar at 66 ± 12 beats/min for Romano-Ward subjects and 64 ± 10 beats/min for controls ($p = 0.8$). Heart rate was insignificantly lower in Romano-Ward subjects than in normals at stage 1 (111 ± 14.8 vs 119 ± 11.8 beats/min [$p = 0.23$]) and at stage 2 (133 ± 17 vs 144 ± 19.6 beats/min [$p = 0.16$]). By stage 3 heart rate in Romano-Ward subjects was significantly lower than in normals (151.6 ± 11.0 vs 169.6 ± 20.4 beats/min [$p = 0.04$]) and during maximal exercise (156 ± 8 vs 182 ± 7.2 beats/min [$p < 0.001$]). Recovery rates in Romano-Ward subjects were the same as in normals.

QT interval response to exercise: The dynamic changes of the QT interval during treadmill exercise are shown in Figure 2. The QT interval of Romano-Ward subjects was significantly longer at each time of measurement than the QT of control subjects. Normals had a progressive decrease in QT length throughout exercise. Romano-Ward subjects, in contrast, had an ini-

tial shortening of QT at stage 1, but essentially no further shortening at subsequent stages of exercise, even though heart rate continued to increase. Also, QT in the Romano-Ward patients returned to the resting control value more quickly than in normals — 3 minutes after exercise — even though the heart rate had not returned to baseline (Figure 1). These findings demonstrate that Romano-Ward subjects have abnormal dynamic control of the QT interval and abnormal QT cycle-length relations during both exercise and recovery. To further evaluate the QT response during exercise, the QT was plotted against heart rate (rather than stage of exercise); the curves for Romano-Ward patients and normals were essentially the same as the QT versus stage of exercise (Figure 2). The QT shortened linearly with heart rate increment in the normals, but in the Romano-Ward patients the QT showed a plateau above a heart rate of 115 beats/min. Also, the QTc of Romano-Ward patients and controls was plotted against the stage of exercise (Figure 3). The QTc of normals during exercise and recovery showed no signi-

FIGURE 4. QT/QS2 ratio during bicycle exercise. The data represent the mean ratio \pm standard error. The QT/QS2 ratio increased significantly during exercise (compared with rest values) in both subjects with the Romano-Ward syndrome (RWS) and in normals (NORM). In subjects with RWS, however, there was a 30% increase in the ratio vs 15% in normals; $p = 0.003$. The ratio of subjects with RWS was higher than in normals at rest and at each stage of exercise and recovery; $p < 0.005$ at all times except sitting (Sit) and at 3 minutes of exercise (0.02). 1'p, 3'p, 5'p, 8'p = 1, 3, 5 and 8 minutes after exercise, respectively; 3', 6', 9', 12' = duration of exercise; Sup = supine.

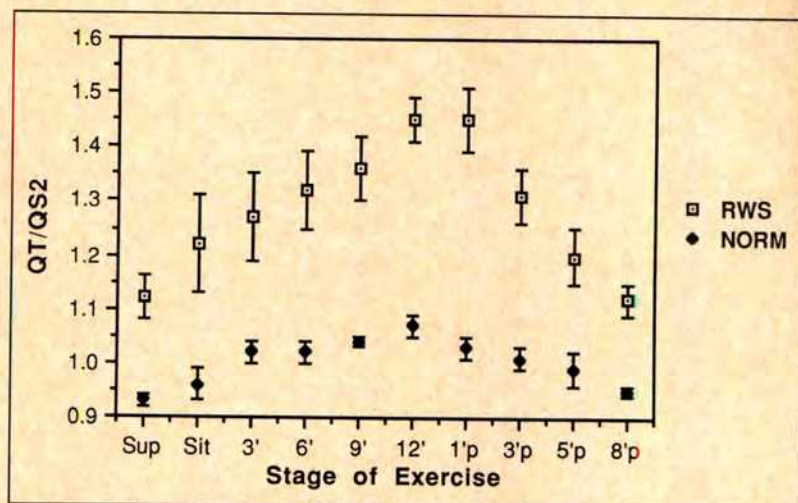
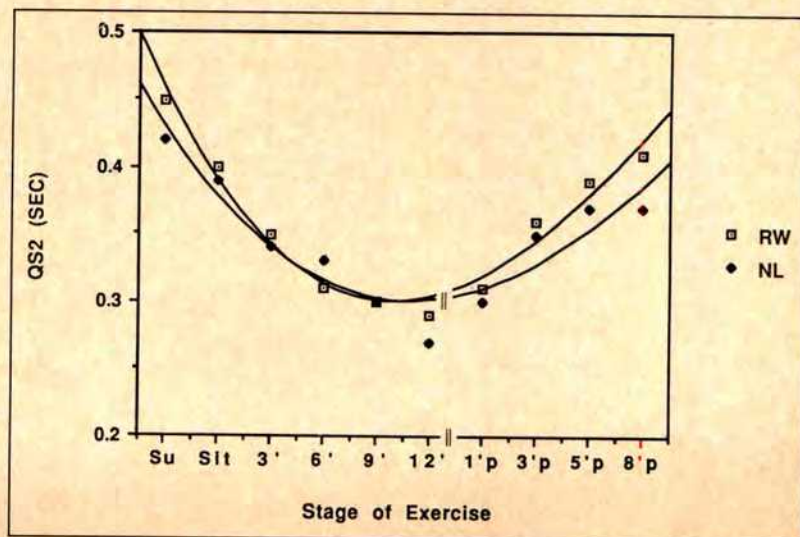


FIGURE 5. QS2 interval during bicycle exercise. The mean QS2 interval shortened similarly in subjects with Romano-Ward syndrome (RW) and in normals (NL) during exercise, and there was no difference in RW QS2 compared with normals at any point of comparison. Su = supine; other abbreviations as in Figure 4.



ficant change from the rest value. In contrast, the QTc in Romano-Ward subjects progressively increased throughout exercise, and was significantly different from the rest QTc ($p < 0.002$ at stage 3 and maximal exercise) and throughout recovery ($p < 0.03$). In addition to the QTc lengthening during exercise, the QTc further increased during recovery, a finding consistent with the abnormal response of the QT interval during recovery (Figure 3).

QT/QTc ratio during bicycle exercise: The QT/QTc ratios of the Romano-Ward syndrome and control groups are shown in Figure 4. The control group had a normal response, with a supine rest ratio of 0.93 ± 0.03 increasing to 1.07 ± 0.05 ($p = 0.003$ compared with rest value) at 12 minutes of exercise, and decreasing to < 1.0 at 5 minutes of recovery. At supine rest, the ratio of Romano-Ward subjects was 1.12 ± 0.11 vs 0.93 ± 0.03 in normals, $p = 0.001$. With sitting, the ratio of Romano-Ward subjects increased to 1.21 ± 0.2 , whereas the ratio in controls was unchanged at 0.96 ± 0.06 ; however, this different response did not reach statistical significance. At peak exercise, the QT/QTc ratio of Romano-Ward subjects increased to 1.45 ± 0.12 ($p = 0.002$ compared with rest value). This represented a 30% increase in the QT/QTc ratio compared with 15% (0.93 to 1.07) in normals ($p = 0.003$). The mechanism of the marked increase in QT/QTc ratio was the failure of the Romano-Ward QT interval to shorten normally during exercise as previously discussed and demonstrated in Figure 2 from the treadmill exercise studies. The same response was seen in this group of subjects undergoing bicycle exercise. The QTc interval, in contrast, shortened the same manner in Romano-Ward subjects and normals (Figure 5) ($p =$ not significant at all points).

QT/QTc in Romano-Ward syndrome subjects with borderline QTc intervals at rest: Evaluation of the resting and exercise QT/QTc ratios in the 2 Romano-Ward syndrome subjects with borderline QTcs at rest showed rest ratios of 0.97 and 1.1 , increasing to 1.33 and 1.62 , respectively, at 12 minutes of exercise.

Ventricular arrhythmias: No ventricular arrhythmias occurred during these studies. This result is possibly related to the selection of the candidates.

DISCUSSION

Heart rate during exercise: Schwartz et al⁶ initially observed low resting heart rates, and suggested this might indicate right cardiac sympathetic deficiency since the cardiac chronotropic fibers exist in the right cardiac nerves.¹⁶⁻¹⁷ We confirmed lower resting heart rates in Romano-Ward subjects younger than age 5 years; however, older Romano-Ward subjects had normal rates, presumably due to the parasympathetic rather than sympathetic control of resting rate, as in

normals,¹⁸ and therefore their sympathetic deficiency was not evident by evaluation of resting heart rate. The lower than normal exercise heart rates seen in the present study confirms a similar chronotropic deficiency in older subjects with Romano-Ward syndrome.

Several previous case reports have described low level, uncontrolled exercise tests in Romano-Ward patients, but no conclusions regarding heart rate response can be made from these data.^{6,19-23} Curtiss et al⁷ studied 3 subjects with a long QT and 8 normals using Bruce treadmill tests. The maximal heart rate of those with Romano-Ward syndrome was 178 beats/min and of normals 188 beats/min, but no statistical comparison was given. The age ranges of the Romano-Ward subjects versus normals were quite disparate, and the groups did not appear to be comparable; thus, no conclusion can be reached concerning heart rate response. An abstract by Locati et al²⁴ reported a lower heart rate in subjects with Romano-Ward syndrome compared to normals during mild bicycle exercise, but 42% of Romano-Ward subjects were taking β blockers, making a comparison of heart rate response in the two groups impossible.

Our results also show that the increase in heart rate during early exercise was similar in Romano-Ward subjects and normals (Figure 1). Early heart rate increment is due to vagal withdrawal^{18,25,26} and it appears to occur normally in the Romano-Ward subjects. Sympathetic stimulation of heart rate occurs at a later stage of exercise,^{18,25,26} and the lower heart rate of Romano-Ward subjects at stage ≥ 3 is consistent with an abnormal sympathetic effect. The lower maximal heart rate seen in the Romano-Ward subjects is similar to that found by Schwartz²⁷ in dogs after right stellectomy, an experimental preparation which may simulate the Romano-Ward syndrome physiology.

QT interval and QT/QTc ratio: The relation between QT interval and exercise heart rate in the inherited long QT syndrome has not been systematically studied previously, but an abnormal relation has been described in several case reports, including lengthening of the QT during exercise.^{1,20,22,28} Our results show the QT to shorten during early exercise, up to a heart rate of approximately 115 beats/min, after which the QT remains rather constant despite increments in heart rate. In contrast, mechanically, the QTc interval, shortens normally in response to rate increment. This failure of the QT to shorten normally leads to the progressively lengthening QTc and QT/QTc ratio; these findings further support an abnormality of sympathetic effect.¹³⁻¹⁵ In addition to increasing our understanding of the physiology of this syndrome, the results may provide a basis for improved diagnosis. Normal subjects are reported to have resting QT/QTc ratios of < 1.0 .¹³⁻¹⁵ It has been suggested that a ratio > 1.0 is

always abnormal and may indicate the presence of some form of the acquired or inherited Romano-Ward syndrome even when the QT interval is normal.^{13-15,29} Although our data support this concept, a larger number of subjects need to be studied for confirmation. However, our data show that a QT/QS2 ratio of <1.0 does not exclude the inherited long QT syndrome, as demonstrated in 1 of our study patients. This patient had a resting supine ratio of 0.97 at the time of the study. Prior electrocardiograms had demonstrated a modestly prolonged QTc, and this patient had a history of earlier syncopal spells, a parent with a long QT interval, and children with clearly prolonged QT intervals. Exercise increased his QT/QS2 ratio to 1.33, with an obviously prolonged QT interval, making the electrocardiographic diagnosis clear. Based on our findings, several suggestions may be offered for diagnostic criteria, but all will need more evaluation. A resting QT/QS2 >1.0 , as previously suggested, may indicate some form of the prolonged QT syndrome. An exercise QT/QS2 ratio >1.17 , which is the mean ± 2 standard deviations of the normal group, may indicate the Romano-Ward syndrome. The maximal ratio in the normal group was 1.14, and the minimal ratio in the Romano-Ward syndrome group was 1.27, supporting 1.17 as a useful dividing point. These QT/QS2 measurements, along with failure of the QT to shorten or an increase in QTc may be particularly helpful in establishing the diagnosis in patients with upper normal to borderline prolonged QT intervals. We recognize the limitations inherent in QT measurements, especially during exercise. The low level bicycle protocol avoids T-P fusion, and improves record quality, assisting to some degree. Newly described computer-assisted repolarization measurements³⁰ may help to avoid the uncertainty of the T end point, and could be used in future studies.

Our studies were performed in subjects with the Romano-Ward syndrome. It is not known whether those with the Jervell and Lange-Nielson syndrome would have the same response, or how subjects with the various forms of acquired long QT interval would respond.

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Improved Specificity of Myocardial Thallium-201 Single-Photon Emission Computed Tomography in Patients with Left Bundle Branch Block by Dipyridamole

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Reduced septal uptake of thallium-201 during exercise is frequently observed in patients with left bundle branch block (LBBB) and normal coronary arteries. This may reflect normal coronary autoregulation in response to lower septal oxygen demand; thus, dipyridamole, which uniformly exploits flow reserve, would be more accurate for diagnosis of coronary artery disease (CAD). Sixteen patients with LBBB underwent exercise and dipyridamole thallium-201 single-photon emission computed tomography and coronary angiography within 3 months. Sensitivity for detection of left anterior descending CAD (>50% stenosis) was 0.83 for exercise and 1.00 for dipyridamole. Specificity was 0.30 (visual) or 0.20 (quantitative analysis) for exercise and 0.80 (visual) or 0.90 (quantitative) for dipyridamole ($p < 0.05$). Dipyridamole combined with quantitative analysis also improved specificity of CAD detection overall ($p < 0.01$). These data demonstrate that pharmacologic vasodilation is more accurate than exercise when diagnosing CAD by myocardial perfusion scintigraphy in patients with LBBB.

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Exercise thallium-201 scintigraphy has been recommended for diagnosis of coronary artery disease (CAD) in patients with left bundle branch block (LBBB).¹ Although specialized diagnostic criteria support limited rationale for this,^{2,3} a major shortcoming is the frequent occurrence of false-positive perfusion abnormalities of the ventricular septum.⁴⁻⁶

In the Framingham study, onset of LBBB increased cumulative cardiovascular mortality three- to fourfold.⁷ However, Peter et al⁸ found no mortality at 2 years in LBBB patients with no CAD compared with 37% in those with surgically treated CAD and 55% in those with medically treated CAD. Similarly, although LBBB is a strong predictor of mortality independent of the degree of heart failure and extent of CAD,^{9,10} Rothbart et al³ demonstrated excellent 2-year prognosis in patients "without clinically overt heart disease." Thus, coexistence of CAD has particular prognostic importance in patients with LBBB, and an accurate noninvasive diagnostic test, previously unavailable, would have immediate clinical utility.

Early and abrupt septal contraction often occurs in patients with LBBB.¹¹ Septal motion abnormalities occur often in relation to asynchronous contraction of the right and then the left ventricle in LBBB patients without CAD.^{4,12,13} Thus, we hypothesized that early in systole, segments of the septum generate sufficient tension to overcome only right ventricular rather than left ventricular outflow resistance, as occurs with normal conduction (Figure 1). By virtue of coronary autoregulation,¹⁴ these septal segments would receive less coronary flow than the subsequently activated free wall,⁵ thus causing septal perfusion defects. Exercise, which increases the delay between right and left ventricular activation relative to the duration of systole, would exaggerate these effects to create reversible defects. In contrast, dipyridamole uniformly exploits coronary vasodilatory flow reserve in the absence of CAD.¹⁵ We therefore assessed whether dipyridamole thallium-201 single-photon emission computed tomography (SPECT) affords higher specificity in detecting CAD in patients with LBBB than does exercise, with particu-

TABLE 1 Sensitivity and Specificity of Exercise and Dipyridamole Thallium-201 SPECT in Left Bundle Branch Block

	Sensitivity				Specificity			
	Exercise		Dipyridamole		Exercise		Dipyridamole	
	Visual	Quant.	Visual	Quant.	Visual	Quant.	Visual	Quant.
Patients overall	0.88 (7/8)	0.75 (6/8)	0.75 (6/8)	0.75 (6/8)	0.25 (2/8)	0.12 (1/8)	0.50 (4/8)	0.88* (7/8)
Coronary territories								
LAD	0.83 (5/6)	0.83 (5/6)	1.00 (6/6)	1.00 (6/6)	0.30 (3/10)	0.20 (2/10)	0.80† (8/10)	0.90* (9/10)
LC	0.50 (1/2)	0.50 (1/2)	0.50 (1/2)	0.50 (1/2)	1.00 (14/14)	0.93 (13/14)	0.93 (13/14)	0.71 (10/14)
Right	0.50 (1/2)	0.50 (1/2)	0.50 (1/2)	0.50 (1/2)	0.43 (6/14)	0.57 (8/14)	0.57 (8/14)	0.57 (8/14)
Total	0.70 (7/10)	0.70 (7/10)	0.80 (8/10)	0.80 (8/10)	0.61 (23/38)	0.61 (23/38)	0.76 (29/38)	0.71 (27/38)

*p < 0.01 compared with values for exercise; †p < 0.05 compared with values for exercise.

LAD = left anterior descending artery; LC = left circumflex artery; Quant. = quantitative analysis; SPECT = single-photon emission computed tomography; Visual = visual analysis.

lar focus on the perfusion territory of the left anterior descending coronary artery that includes the ventricular septum.

METHODS

Study group: Patients with LBBB who underwent exercise thallium-201 SPECT and coronary angiography within 3 months were asked to undergo dipyridamole thallium-201 SPECT during this period. Electrocardiograms were analyzed according to the criteria of Freedman et al.⁹ Informed written consent was obtained.

Exercise thallium-201 SPECT: Patients underwent a symptom-limited Bruce protocol treadmill exercise test. Medications were continued or withheld for testing on the advice of referring physicians. At peak exercise, 3 mCi of thallium-201 was injected and exercise was continued for 1 minute. Imaging was performed 10 minutes and 4 hours after thallium-201 injection, using 60 projections, 3° per step, over a 180° clockwise circular orbit beginning at a 45° right anterior oblique projection. Total imaging time was 15 minutes. The detector had a 3/8-inch sodium iodide crystal and low-energy all purpose collimator. A 30% window on the 67-keV photopeak and on the 169-keV photopeak were used. Images were stored in 64 × 64 matrixes. Back projection used the product of a Ramp and modified Hanning filter described as: $f \cdot (0.5 + 0.5 \cos [\pi(f/f_m)^b])^c$ where f = frequency, f_m = Nyquist frequency, $b = 2.5$ and $c = 5$.

Coronary angiography: Each opacified epicardial vessel was recorded in >1 nearly orthogonal projection. Interpretation was by visual consensus of 2 observers unaware of patient data. Stenoses between 30 and 70% in diameter were visually measured by computerized caliper (Sandhill). Stenoses >50% in diameter, averaged in 2 views, were considered significant.

Dipyridamole thallium-201 SPECT: Patients had a 4-minute intravenous infusion of 0.56 mg/kg of dipyridamole. Ten minutes after infusion, 3 mCi of thallium-201 was injected. Image acquisition began 10 minutes later. Redistribution imaging was performed 4 hours after thallium-201 injection. Processing was performed as for exercise SPECT.

Scintigraphic analysis: Oblique short-axis and horizontal and vertical long-axis tomograms were scored (3 = normal, 2 = mild/moderately reduced, 1 = moderately/severely reduced, 0 = no uptake) by consensus of 2 observers unaware of other patient data. Activity scores were assigned to 9 myocardial segments (antero-apical, anterobasal, apicolateral, basal lateral, infero-apical, inferobasal, apical septum, basal septum and apex) to derive a consensus of 0-, 1-, 2- or 3-vessel CAD and CAD location (left anterior descending = anteroapical and apex; left circumflex = lateral; right = inferoapical). Quantitative analysis compared polar plots with normal data as previously described.¹⁶ Sig-

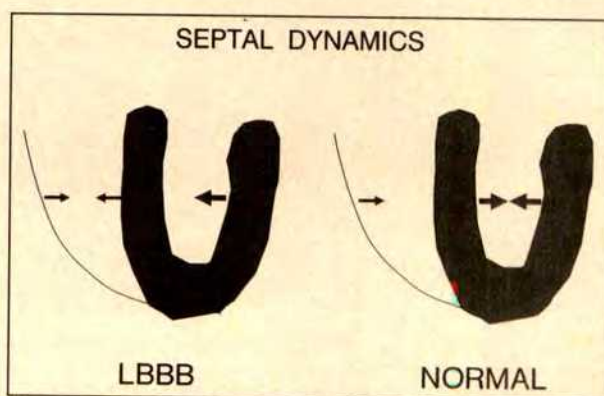


FIGURE 1. Schematic of septal dynamics associated with left bundle branch block (LBBB). In early systole the septum contracts with low tension to overcome right ventricular outflow resistance, whereas with normal conduction tension is higher to overcome left ventricular outflow resistance.

nificant CAD was detected when exercise activity was >2.5 standard deviations below the mean of normal over a continuous area $>4\%$ of the left ventricular myocardium.

Statistical analysis: Sensitivity and specificity were calculated by standard formulas, and were compared using Fisher's exact test. Differences were considered significant if $p < 0.05$.

RESULTS

Sixteen patients (11 men and 5 women, mean age \pm standard deviation 63 ± 8 years [range 51 to 69]) completed the protocol. Presenting clinical problems leading to exercise thallium-201 scintigraphy and coronary angiography were: typical angina (9 patients), atypical angina (2 patients), atypical chest pain (2 patients), left ventricular dysfunction (without CAD, 2

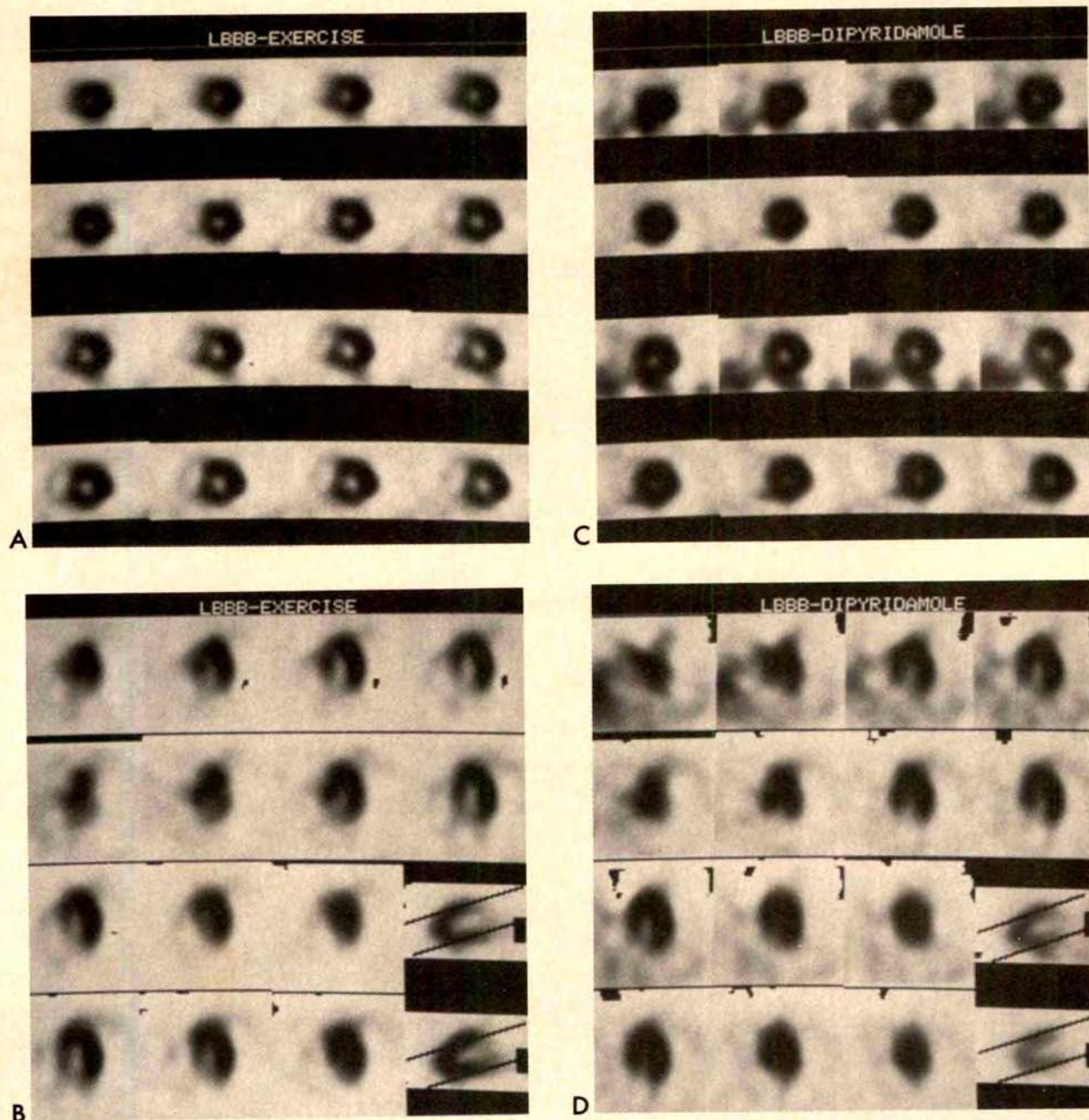


FIGURE 2. A, exercise thallium-201 tomograms of a patient with left bundle branch block (LBBB) with normal coronary arteries (oblique short-axis reconstruction). Exercise (rows 1 and 3) and redistribution (rows 2 and 4) arranged from apex (upper left) to base (lower right). A partially reversible septal perfusion defect is seen between 7 and 10 o'clock. B, horizontal long-axis reconstruction (companion to A) arranged from inferior wall (upper left) to anterior wall (lower right). Partially reversible septal defect is seen on left in stress tomograms. C, dipyridamole thallium-201 tomograms of same patient (images as in A [dipyridamole rows 1 and 3, redistribution rows 2 and 4]). Septal perfusion is normal. D, horizontal long-axis (companion to C) images as in B. Septal perfusion is normal.

patients) and previous myocardial infarction (1 patient). Mean exercise time was 7.2 ± 2.2 minutes, sufficient to achieve mean peak heart rate of 139 ± 23 minutes. Exercise was terminated because of fatigue (10 patients), dyspnea (4 patients) or chest pain (2 patients). Eight patients had significant CAD (2 multivessel, 6 single vessel). Sensitivity and specificity for CAD detection (visual and quantitative) during exercise and dipyridamole therapy are listed in Table I. Dipyridamole was superior to exercise with respect to specificity of CAD detection overall by quantitative analysis. This was also true in relation to specificity for detection of left anterior descending disease, both visually (Figure 2) and quantitatively. There were 7 visually false-positive exercise defects in the left anterior descending territory (4 reversible, 2 partially reversible, 1 fixed). Two were septal and 5 were anteroseptal.

DISCUSSION

Our first reports of improved specificity of CAD detection in patients with LBBB by dipyridamole^{17,18} were followed by similar observations from other centers. Morais et al¹⁹ noted fewer false-positive studies with dipyridamole than with exercise in 9 patients undergoing both tests, but only 5 underwent angiography.

There is possible bias implicit in the false-positive rates of exercise studies reported by DePuey et al⁶ (90%) and ourselves (75% visual) in that these patients were selected to undergo coronary angiography. Jazmati et al²⁰ reported on 93 consecutive patients with LBBB who underwent exercise thallium-201, and only 13 (14%) had septal defects. They had limited angiographic data and could not refute the reported high prevalence of false-positive thallium studies, but concluded that exercise thallium-201 was a worthwhile test for patients with LBBB because abnormal septal perfusion was uncommon. In our laboratory LBBB was present in 261 of 6,531 (4%) consecutive thallium-201 studies. Of these, 24 were planar and 18 (75%) had septal defects (0 of 1 with dipyridamole, 18 of 23 during exercise [78%]). SPECT was performed in 237 studies and 199 (84%) had septal defects (59 of 74 with dipyridamole [80%], 150 of 163 during exercise [86%]). This suggests a higher prevalence of CAD than in Jazmati's cohort. In such referral populations, high specificity will enhance the usefulness of dipyridamole over exercise thallium-201.

Several mechanisms of exercise perfusion defects in patients with LBBB without CAD have been proposed, including prolonged compression of septal perforators,⁵ reduced diastolic flow,²¹ small vessel CAD,³ septal fibrosis²¹ and wall motion artifact.^{23,24} The finding by Hirzel et al⁵ of diminished septal perfusion using micro-

spheres in dogs during right ventricular pacing to simulate LBBB is consistent with diminished septal perfusion with this abnormal conduction pattern. Regional myocardial metabolic abnormalities may coexist, providing another mechanism.¹⁰

Reversible and fixed false-positive septal defects were observed in this study and others.^{19,20} False-positive dipyridamole studies also occurred. This might occur as a wall motion artifact; however, our hypothesis—that defects arise due to ventricular asynchrony, unequal systolic wall tension, and unequal perfusion governed by autoregulation—lends itself to further speculation. Although myocardial fibrosis could lead to secondary development of LBBB, alternatively longstanding LBBB could cause septal thinning analogous to "disuse atrophy." In this context, it will be interesting to examine whether new-onset LBBB is associated with reversible exercise septal defects and normal dipyridamole studies, which progress to fixed exercise or dipyridamole septal defects (with septal thinning), or both, occurring later as a sign of chronic conduction delay. Also, with relation to true-negative LBBB exercise thallium-201 studies, the septum may be activated without delay by "arborization block"¹¹ and septal motion may be normal.¹³

Identification of CAD in patients with LBBB has major prognostic importance, and we believe that the diagnostic accuracy of dipyridamole thallium-201 SPECT establishes this modality as a preferred noninvasive diagnostic test. Our results are consistent with the more general hypothesis that pharmacologic vasodilation and use of a tracer with uptake related to flow are required for accurate noninvasive diagnosis of CAD in patients with LBBB. We therefore anticipate that adenosine stress and technetium-99m sestamibi and teboroxime will have comparable diagnostic accuracy.

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Hemodynamic Effects of Celiprolol in Essential Hypertension

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The immediate and short-term (2 week) hemodynamic and humoral effects of the β_1 antagonist, β_2 agonist, celiprolol, were compared with those of more prolonged atenolol therapy in 12 patients with essential hypertension. Celiprolol produced an immediate dose-dependent decrease in mean arterial pressure (113 ± 3 to 102 ± 2 mm Hg; $p < 0.001$) and total peripheral resistance (49 ± 3 to 38 ± 1 U/m²; $p < 0.005$) that was associated with an increased heart rate (67 ± 1 to 73 ± 2 beats/min; $p < 0.01$) and cardiac index ($2,347 \pm 129$ to $2,708 \pm 111$ ml/min/m²; $p < 0.01$). Both celiprolol and atenolol reduced mean arterial pressure with short-term treatment ($p < 0.01$); this was associated with a reduced total peripheral resistance with celiprolol (from 24 ± 1 to 21 ± 1 U/m²; $p < 0.02$) and was not observed with atenolol. Moreover, in contrast with atenolol, celiprolol did not change heart rate or stroke and cardiac indexes. Splanchnic and forearm vascular resistances decreased with celiprolol ($p < 0.05$) but not with atenolol; neither β -blocking drug altered renal blood flow. These results demonstrate that the hemodynamic effects of celiprolol were strikingly different from atenolol; celiprolol reduced arterial pressure and total peripheral and certain vascular resistances without altering heart rate, cardiac index or regional blood flows. These effects may be explained by celiprolol's cardiac β_1 receptor inhibitory and peripheral β_2 receptor agonistic effects.

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Beta-adrenergic receptor blocking agents have been used for >25 years for the safe and effective treatment of hypertension,¹ although they are contraindicated in some patients because of some of their cardiopulmonary effects.² A new diethylurea-substituted β -adrenergic receptor blocking agent, celiprolol, offers some novel pharmacologic features that may obviate some of these contraindications because of its β_2 adrenergic receptor agonistic and intrinsic sympathomimetic activity in addition to its β_1 adrenergic receptor inhibitory actions.^{3,4} This report details the immediate (i.e., intravenous) and short-term (2 weeks) hemodynamic and humoral effects of celiprolol, comparing them in the same patients with mild to moderate essential hypertension who had responded to treatment with atenolol, an established β -blocker.

METHODS

Patients: Twelve patients (8 men, 8 white) with mild to moderately severe essential hypertension whose ages ranged from 40 to 70 years (average 50 ± 3) were studied. Each patient provided informed consent to a protocol previously approved by our institution's human use committee. Their body mass indexes, mean arterial pressures and heart rates were 29.0 ± 2.3 kg/m², 115 ± 3 mm Hg, and 67 ± 2 beats/min, respectively. Patients were included in the study if their clinical evaluation failed to demonstrate a specific cause for their hypertension, there was no evidence of target organ involvement, and during the placebo washout period of 3 weeks, supine diastolic pressures decreased to between 90 and 114 mm Hg. Their clinical evaluation included history, physical examination, electrocardiogram, chest roentgenogram, complete laboratory screening (hemogram, automated battery of blood chemistry, urinalysis), and noninvasive hemodynamic evaluation determined using 2-dimensional-guided M-mode echocardiography. Moreover, only patients were included who had responded to prior β -adrenergic receptor inhibitory therapy (with atenolol) in order that the hemodynamic responses to celiprolol could be compared with responses to atenolol.

Protocol: The study was designed as a single-blind, placebo-controlled trial. During the first period (phase I) all patients had been receiving atenolol for ≥ 3 months. The average daily dose of atenolol for the most

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TABLE I Immediate Hemodynamic Effects After Low (n = 4) and High (n = 8) Doses of Celiprolol Infusion

	Saline Control	Celiprolol (mg/kg, intravenous)		
		0.07	0.14	0.28
Low Doses				
Arterial pressures (mm Hg)				
Systolic	148 ± 6	148 ± 5	145 ± 9	143 ± 6*
Diastolic	95 ± 2	95 ± 2	91 ± 3	89 ± 2†
Mean	113 ± 4	113 ± 3	109 ± 4	107 ± 3†
Heart rate (beats/min)	64 ± 1	67 ± 2	68 ± 2	70 ± 2
Stroke index (ml/beat/m ²)	36 ± 4	38 ± 2	37 ± 2	38 ± 2
Cardiac index (ml/min/m ²)	2,295 ± 218	2,540 ± 103	2,505 ± 121	2,644 ± 87
Total peripheral resistance index (U/m ²)	51 ± 3	45 ± 3	44 ± 3	41 ± 2
High Doses				
Arterial pressures (mm Hg)				
Systolic	147 ± 5	134 ± 4	129 ± 4†	129 ± 4*
Diastolic	95 ± 4	85 ± 4*	85 ± 2*	82 ± 2*
Mean	112 ± 3	101 ± 4*	99 ± 3*	98 ± 3*
Heart rate (beats/min)	68 ± 2	71 ± 2†	70 ± 2	73 ± 2†
Stroke index (ml/beat/m ²)	36 ± 2	36 ± 2	40 ± 1	39 ± 2
Cardiac index (ml/min/m ²)	2,445 ± 154	2,545 ± 142	2,757 ± 83	2,829 ± 145†
Total peripheral resistance index (U/m ²)	47 ± 1	42 ± 2	37 ± 1†	35 ± 1*

*p < 0.01; †p < 0.05.
Values are mean ± standard error of the mean.

*p < 0.01; †p < 0.05.

Values are mean ± standard error of the mean.

recent 4 weeks of treatment was 50 to 100 mg (average 65 ± 8). At the end of this atenolol period (phase I), the first hemodynamic evaluation was obtained and the atenolol dose was tapered and withdrawn to permit entrance into a 3-week placebo period (phase II). At the end of phase II, a second series of hemodynamic studies was performed, after which celiprolol was administered intravenously. This was achieved by slowly infusing 10 ml of saline solution (0.9%), followed by 3 successive celiprolol injections calculated to deliver 0.071, 0.071 and 0.142 mg/kg to 4 patients and 0.106, 0.106 and 0.212 mg/kg to 8 patients. In 1 patient the infusion was terminated after the initial 0.106-mg/kg dose because arterial pressure had been reduced to normotensive levels. Each dose was administered over a 5-minute period, then followed by a 10-minute observation period to establish hemodynamic stability. During the 2-week oral celiprolol period (phase III), all patients received 400 mg once daily, at the end of which the third hemodynamic evaluation was obtained.

Each of the 3 hemodynamic evaluations, which included humoral measurements, was performed after an overnight fast and involved insertion of a venous line for withdrawal of blood samples and regional blood flow studies. All procedures were obtained after at least 1 hour of rest in the supine position.

Echocardiographic recordings were obtained with an ultrasonoscope (model SSH-60A, Toshiba) interfaced with a line scan recorder (LSR-20B) and probes

of either 2.5 or 3.75-MHz frequency. The technique for visualization of the left ventricle has been described in detail.⁵ In brief, left ventricular wall thicknesses and dimensions were measured.⁶ End-systolic and end-diastolic volumes were calculated,⁷ and cardiac output was determined by multiplying end-systolic-diastolic volume differences by heart rate. This noninvasive determination of cardiac output estimated by echocardiography correlates closely with concomitant indicator-dilution measurements obtained with indocyanine green dye dilution curves.⁵ Total peripheral resistance was calculated from the mean arterial pressure (diastolic pressure plus one-third of pulse pressure) divided by cardiac output. Left ventricular mass was determined by corrected criteria proposed by Devereux.⁸ Left ventricular systolic functions were assessed from measurements of cardiac output, fractional fiber shortening, ejection fraction and velocity of circumferential shortening.⁹⁻¹¹ Left ventricular preload was assessed as end-diastolic volume divided by body surface area, and wall stress was used as an index of afterload.¹² Diastolic functions were determined by computer assisted analyses (model DPS/EC 500, Digisonics, Houston, Texas).¹³ All echocardiograms were read independently by 2 investigators with interobserver variability for septal thickness and other measurements being 6 to 8%, respectively.⁹ Reproducibility of measurements, as assessed by correlation between 2 echocardiographic readings obtained 30 minutes apart, were close for sys-

TABLE II Immediate Hemodynamic and Humoral Effects of Celiprolol Infusion in 12 Patients

	Saline	Maximal Dose*	p Value
Hemodynamics			
Arterial pressures (mm Hg)			
Systolic	148 ± 4	134 ± 4	<0.01
Diastolic	95 ± 3	84 ± 2	<0.001
Mean	112 ± 3	101 ± 2	<0.001
Heart rate (beats/min)	67 ± 1	73 ± 2	<0.01
Stroke index (ml/m ²)	35 ± 2	37 ± 2	NS
Cardiac index (ml/min/m ²)	2,347 ± 129	2,708 ± 111	<0.01
Total peripheral resistance index (U/m ²)	49 ± 3	38 ± 1	<0.005
Forearm Hemodynamics			
Total forearm flow	5.4 ± 0.5	6.4 ± 0.7	<0.05
Total forearm vascular resistance	23 ± 2	18 ± 2	<0.001
Skeletal muscle blood flow (ml/100 ml/min)	4.1 ± 0.4	5.0 ± 0.7	<0.01
Skeletal muscle vascular resistance (U)	32 ± 4	24 ± 3	<0.01
Skin blood flow (ml/100 ml/min)	1.3 ± 0.1	1.2 ± .02	NS
Skin vascular resistance (U)	134 ± 32	130 ± 35	NS
Echocardiographic Data			
End-diastolic volume index (ml/m ²)	55.2 ± 3	55.0 ± 3	NS
End-systolic wall stress (10 ³ dynes/cm ²)	44 ± 4	36 ± 3	<0.01
Ejection fraction (%)	65 ± 3	69 ± 3	NS
Fractional fiber shortening (%)	36 ± 2	39 ± 2	NS
Velocity of circumferential fiber shortening (circ./s)	1.2 ± 0.1	1.3 ± 0.1	NS
End-systolic wall stress/end-systolic volume index (10 ³ dynes cm ² /ml·m ²)	2.3 ± 0.1	2.2 ± 0.1	NS
Humoral Substances			
Norepinephrine (pg/ml)	241 ± 28	332 ± 33	<0.02
Epinephrine (pg/ml)	39 ± 5	42 ± 6	NS
Plasma renin activity (mg/ml/hour)	1.1 ± 0.2	0.8 ± 0.1	NS

*Intravenous administration of 0.284 and 0.424 mg/kg of celiprolol in 4 and 7 patients, respectively; of the latter 7 patients, 1 received only 0.106 mg/kg. Values are mean ± standard error of the mean. circ. = circumference; NS = not significant.

tolic dimensions and other measurements ($r = 0.86$ and 0.90), respectively.¹⁴

Plasma volume was measured with I¹²⁵-labeled human serum albumin,¹⁵ and total blood volume was calculated from plasma volume and hematocrit. Renal blood flow was determined from measuring the clearance of I-labeled para-aminohippurate.^{15,16} Glomerular filtration rate was calculated from 24-hour endogenous creatinine clearance. Splanchnic blood flow was determined from the plasma clearance of 50 mg indocyanine green dye and hematocrit.¹⁷ Total forearm blood flow (including skeletal, muscular and cutaneous blood flows) were estimated from the increased forearm volume during venous occlusion before and after excluding hand blood flow.^{14,18} The difference between total forearm and hand-excluded flows represent skeletal muscle flow; hand flow is considered to be primarily skin flow.¹⁴ Three to 5 successive forearm flow measurements were obtained in each patient and averaged in order to obtain these flow measurements. Plasma catecholamine levels¹⁹ and plasma renin activity²⁰ were determined from venous blood withdrawn 30 minutes af-

ter supine rest and were measured by the radioenzymatic and radioimmunoassay methods, respectively.

To demonstrate statistical significance, a 1-way analysis of variance for repeated measurements was used with subsequent paired comparison with the Bonferroni-Holm correction.²¹ All results are presented as mean ± 1 standard error of the mean.

RESULTS

Immediate effects: Intravenous administration of the 3 incremental low and the 3 incremental high celiprolol doses over 35 minutes reduced systolic, diastolic and mean arterial pressure in all patients. However, 1 patient received only the initial (of the high) dose sequence because her arterial pressure was reduced immediately to normotensive levels. The hemodynamic effects of the successive low (4 patients) and higher dose (8 patients) sequences of intravenous celiprolol are listed in Tables I and II. Systolic, diastolic and mean arterial pressures were reduced by 10 ($p < 0.01$), 12 ($p < 0.001$), and 10% ($p < 0.01$), respectively. This was associated with a 9 and 15% increases in heart rate and

TABLE III Hemodynamic Indexes After Short-Term Treatment with Atenolol, Placebo and Celiprolol in 12 Patients with Essential Hypertension

	Atenolol	Placebo	Celiprolol	Values		
				p1	p2	p3
Arterial pressures (mm Hg)						
Systolic	134 ± 3	148 ± 4	136 ± 3	<0.01	<0.01	NS
Diastolic	90 ± 2	95 ± 3	89 ± 1	NS	<0.05	NS
Mean	105 ± 2	113 ± 3	104 ± 1	<0.02	<0.01	NS
Heart rate (beats/min)	58 ± 3	67 ± 1	70 ± 2	<0.01	NS	<0.001
Stroke index (ml/beat/m ²)	38 ± 2	35 ± 2	37 ± 2	NS	NS	NS
Cardiac index (ml/min/m ²)	2,160 ± 100	2,350 ± 130	2,530 ± 110	NS	NS	<0.05
Total peripheral resistance index (U/m) ²	25 ± 2	24 ± 1	21 ± 1	NS	<0.02	<0.01
Humoral substances and blood volumes						
Total blood volume (ml)	4,732 ± 265	5,104 ± 265	4,996 ± 321	NS	NS	NS
Total plasma volume (ml)	2,945 ± 162	3,103 ± 161	3,115 ± 195	NS	NS	NS
Norepinephrine (pg/ml)	287 ± 44	233 ± 26	260 ± 25	NS	NS	NS
Epinephrine (pg/ml)	37 ± 6	35 ± 5	34 ± 8	NS	NS	NS
Plasma renin activity (ng/ml/hour)	1.0 ± 0.2	1.0 ± 0.1	1.4 ± 0.3	NS	NS	NS

Values are mean ± standard error of the mean.

p1 = atenolol versus placebo; p2 = celiprolol versus placebo; p3 = atenolol versus celiprolol; NS = not significant.

TABLE IV Regional Hemodynamics and Renal Function After Short-Term Treatment with Atenolol, Placebo and Celiprolol

Vascular bed	Atenolol	Placebo	Celiprolol
Splanchnic			
Blood flow (ml/min)	588 ± 41	680 ± 43	759 ± 61
Vascular resistance (U)	19 ± 2	17 ± 1	15 ± 1*
Forearm			
Total forearm			
Blood flow (ml/100 ml/min)	5.0 ± 0.6	5.3 ± 0.5	5.7 ± 0.5
Vascular resistance (U)	31.6 ± 4	31.9 ± 4	25.5 ± 2*
Skin			
Blood flow (ml/100 ml/min)	1.2 ± 0.2	1.2 ± 0.1	1.3 ± 0.1
Vascular resistance (U)	127 ± 23	134 ± 32	88 ± 13*
Skeletal muscle			
Blood flow (ml/100 ml/min)	3.8 ± 0.5	4.1 ± 0.4	4.4 ± 0.4
Vascular resistance (U)	32 ± 3	32 ± 4	26 ± 2*
Renal			
Blood flow (ml/min)	766 ± 38	842 ± 65	800 ± 58
Vascular resistance (U)	14 ± 1	14 ± 1	14 ± 1
Glomerular filtration rate (ml/min)	108 ± 6	113 ± 7	111 ± 6
Filtration fraction (%)	24 ± 1	25 ± 2	25 ± 1
Serum creatinine (mg/dl)	1.04 ± 0.04	1.01 ± 0.07	1.03 ± 0.06
Creatinine clearance (ml/min)	116 ± 8	126 ± 13	116 ± 8
Serum uric acid (mg/dl)	5.6 ± 0.5	5.4 ± 0.4	5.4 ± 0.5

*p < 0.05.

Values are mean ± 1 standard error of the mean.

cardiac index ($p < 0.01$) and a 22% decline in total peripheral resistance index ($p < 0.005$; Table II). Plasma norepinephrine concentration increased after celiprolol ($p < 0.02$) and its associated reduction in arterial pressure. Plasma renin activity did not change.

Forearm muscle flow increased by 22% ($p < 0.01$); this was associated with a 25% reduction in skeletal muscle vascular resistances ($p < 0.01$; Table II). Cutaneous blood flow and vascular resistance remained unchanged.

Left ventricular afterload (end-systolic wall stress) was reduced 18% after administration of intravenous

celiprolol ($p < 0.01$), but left ventricular ejection fraction, fractional fiber shortening rate and the velocity of circumferential shortening remained unchanged (Table II).

Comparative effects of celiprolol and atenolol: Celiprolol (400 mg) and atenolol (65 ± 8 mg, average) were administered once daily; both significantly reduced arterial pressure to comparable levels (Table III). However, arterial pressure reduction with atenolol was associated with a reduced heart rate ($p < 0.001$) and cardiac output (Table III). In contrast to atenolol, the reduced arterial pressure produced by celiprolol was

associated with a reduction in total peripheral resistance index ($p < 0.02$). The faster heart rate and greater stroke index accounted for a higher cardiac index with celiprolol than with atenolol ($p < 0.05$; Table III).

Left ventricular wall thicknesses and mass and diastolic dimension did not change during the 3-week placebo period after atenolol and the short 2-week treatment period of celiprolol. However, splanchnic and forearm (including skeletal muscular and cutaneous) vascular resistances declined with celiprolol but not with atenolol (Table IV). Neither β blocking drug affected renal blood flow. Norepinephrine levels at the conclusion of oral therapy with both agents were similar to the placebo levels, and neither agent expanded intravascular volume (Table III).

DISCUSSION

The results of this study demonstrate that the immediate and short-term hemodynamic effects of the newer β -adrenergic blocking drug, celiprolol, were strikingly different from those reported for the earlier β blockers.²²⁻²⁵ These hemodynamic differences reflect their different pharmacologic properties. Both atenolol and celiprolol have cardioselective β_1 inhibitory properties, but only celiprolol acts as a peripheral β_2 adrenergic receptor agonist having additional intrinsic cardiac sympathetic activity.^{3,4,26,27}

After intravenous administration, propranolol (or other similar agents) reduces heart rate and cardiac output; this is not associated with a decrease in arterial pressure.^{22,26} In contrast, immediately after its intravenous administration, celiprolol reduced arterial pressure. This response was similar to intravenous dilevalol, a pharmacologic agent having similar properties²⁸ and labetalol, a different type of compound having α - as well as β -adrenergic receptor inhibitory properties.²⁹

The immediate pressure decrease with celiprolol persisted with oral therapy, and this remained associated with a reduced total peripheral resistance. Heart rate and cardiac output, which reflexively increased immediately after intravenous celiprolol, was related to increased circulating norepinephrine, changes that reverted to pretreatment levels by the end of the 2 week treatment.

These findings of an immediate reduction in arterial pressure associated with a reduced total peripheral resistance, presumably related to arterial dilation, was confirmed by the reduction in forearm and splanchnic vascular resistances. Forearm resistance reduction had been reported earlier by Mancia et al.³⁰ In contrast to the forearm hemodynamic alterations, renal hemodynamics remained unchanged. These renal hemodynamic findings are similar to those of others who were unable to show renal circulatory changes with more pro-

longed treatment³¹ and to our earlier findings with atenolol²⁵ and nadolol.³²

Finally, the hemodynamic alterations induced by celiprolol were not associated with changes in intravascular volume, a finding that is consistent with that of earlier β -receptor antagonists.^{23-25,32,33} However, in contrast to some of the earlier β -blocking agents, which reduced plasma renin activity,^{23,25} celiprolol had no such effect. The hemodynamic changes produced by intravenous and oral celiprolol, may be explained by its cardiac β_1 receptor inhibitory and peripheral β_2 receptor agonistic effects. These changes suggest a more physiologic action of this new class of β -adrenergic receptor blocking agent for the hypertensive patient: reduction of arterial pressure and vascular resistance without altering heart rate, cardiac output and regional blood flows.

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Use of Valsalva Maneuver to Unmask Left Ventricular Diastolic Function Abnormalities by Doppler Echocardiography in Patients with Coronary Artery Disease or Systemic Hypertension

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It has been suggested that changes in left atrial pressure may mask or mimic left ventricular diastolic function abnormalities detected by Doppler echocardiography. The effect of the Valsalva maneuver on the transmitral flow velocity profile was therefore studied in 28 patients without evidence of coronary artery disease (group 1, mean age \pm standard deviation 50 ± 8 years) and in 94 patients with evidence of coronary artery disease or systemic hypertension (group 2, mean age 54 ± 10 years). At baseline, group 2 patients had higher peak late diastolic filling velocity (A), lower peak early (E) to late diastolic filling velocity (E/A) ratio and longer isovolumic relaxation time than group 1, whereas heart rate, E velocity and E deceleration time were similar in both groups. During Valsalva, both groups had similar increases in heart rate and similar decreases in E velocity but E/A ratio decreased significantly only in group 2 because of a lesser decrease in A velocity. The E/A ratio was ≥ 1.0 both before and during Valsalva in all but 1 patient in group 1, whereas in group 2, 32 patients had E/A ≥ 1.0 at rest and during Valsalva, 33 patients had E/A ≥ 1.0 at rest but < 1.0 during Valsalva and 29 patients had E/A < 1.0 both at rest and during Valsalva. Using group 1 as controls, prevalence, specificity and positive predictive value of E/A < 1.0 in group 2 were 31, 100 and 100% at rest and 66, 96 and 98% during Valsalva. The correct classification of patients in groups 1 and 2 on the basis of E/A ratio < 1.0 was 47% at rest and 73% during Valsalva. This study shows that the Valsalva maneuver is an easy means of obtaining a reduction in left atrial

pressure during Doppler echocardiography and helps unmask otherwise unsuspected diastolic function abnormalities.

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Left ventricular (LV) diastolic function abnormalities have been reported in various forms of heart disease.¹ However, some investigators²⁻⁷ have emphasized that the Doppler transmitral flow velocity profile used to detect such abnormalities is not only sensitive to changes in diastolic function, but also is responsive to changes in pulmonary venous return. Therefore, Choong et al³ suggested that a reduction in left atrial pressure may change the transmitral flow velocity profile in a manner that mimics the abnormalities previously reported with impairment of LV diastolic function, whereas other investigators⁴ reported that an increase in left atrial pressure may mask LV relaxation abnormalities. For these reasons, caution has been advocated when interpreting Doppler-derived indexes of LV diastolic function²⁻⁷; further investigations taking into account the effects of left atrial pressure have been recommended. The Valsalva maneuver is a relatively simple and easily applicable method of acutely reducing venous return.⁸ The objective of this study was to determine if the Valsalva maneuver could help better account for the effect of left atrial pressure on the transmitral flow velocity profile and better differentiate between patients with and without LV diastolic function abnormalities.

METHODS

The study population consisted of 122 consecutive patients (88 men and 34 women) aged 31 to 75 years (mean age \pm standard deviation 53 ± 10) referred to our Nuclear Medicine Laboratory for a treadmill thallium stress test using the standard Bruce protocol. Primary reasons for referral included: atypical chest pain (69 patients of whom 23 had previous evidence of coro-

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TABLE I Baseline Characteristics in Patients Without Evidence of Disease (group 1) and With Evidence of Coronary Artery Disease or Systemic Hypertension (group 2)

Variable	Group 1 (n = 28)	Group 2 (n = 94)	p Value
Age (years)	50 ± 8	54 ± 10	<0.05
Heart rate (beats/min)	69 ± 10	68 ± 13	NS
E velocity (cm/s)	70 ± 13	69 ± 16	NS
A velocity (cm/s)	53 ± 15	60 ± 20	<0.05
E/A ratio	1.4 ± 0.3	1.2 ± 0.5	<0.01
E deceleration time (ms)	187 ± 40	197 ± 58	NS
Isovolumic relaxation time (ms)	80 ± 8	96 ± 16	<0.001

Values are mean ± 1 standard deviation.
A velocity = peak late diastolic filling velocity; E velocity = peak early diastolic filling velocity. NS = not significant.

nary artery disease), typical angina pectoris (24 patients), previous myocardial infarction (16 patients), previous coronary artery bypass surgery or angioplasty (13 patients).

Doppler echocardiographic examinations were performed on either an ATL Mark 600, a Hewlett-Packard model 77020A or a Toshiba model SSH165 ultrasound system. The study was performed on the same day as the stress test during the period between the thallium scans performed immediately and 4 hours after the stress test. No patient had to be excluded because of a technically inadequate study; all patients were in normal sinus rhythm and none had evidence of significant valvular disease. Measurements were obtained by 2 independent observers who had no knowledge of the clinical history or the results of the stress test, and disagreements were resolved by consensus. Measurements obtained for the purpose of the study included peak E velocity (peak transmitral flow velocity during early diastole), peak A velocity (peak transmitral flow velocity during late diastole), deceleration time (time elapsed between peak E velocity and the point where the extrapolation of the deceleration slope of the E velocity crosses the zero baseline), and isovolumic relaxation time (time elapsed between aortic valve closure and mitral valve opening). Peak E and A velocities and E deceleration time were obtained from pulsed-wave Doppler recordings in the apical 4-chamber view with the sample volume placed at the tip of the mitral valve where the mitral flow velocity signal is the highest. Isovolumic relaxation time was obtained from continuous-wave Doppler recordings in the apical window with the ultrasound beam intersecting both LV outflow tract velocity signal and mitral flow velocity signal as previously described. All recordings were performed at a paper speed of 50 or 100 mm/s, and 3 consecutive beats were analyzed for each variable. To minimize the effects of

TABLE II Changes from Baseline During Valsalva Maneuver

Variable	Group 1 (n = 28)	Group 2 (n = 94)	p Value
Heart rate (beats/min)	+3 ± 7*	+2 ± 9*	NS
E velocity (cm/s)	-20 ± 8†	-22 ± 10†	NS
A velocity (cm/s)	-13 ± 10†	-4.5 ± 13‡	<0.001
E/A ratio	-0.1 ± 0.3	-0.3 ± 0.3†	<0.01
E deceleration (ms)	+21 ± 62	+45 ± 67†	NS
Isovolumic relaxation time (ms)	+15 ± 7†	+18 ± 14†	NS

Values are mean ± 1 standard deviation.
Significance of changes within each group: *p < 0.05; †p < 0.001; ‡p < 0.01.
NS = not significant.

respiration, baseline measurements were obtained while the patient was asked to briefly stop breathing at end expiration. The same measurements were then repeated during phase II of the Valsalva maneuver. Particular care was taken to ensure that the pulsed Doppler sample volume remained positioned as mentioned before and still recorded the highest transmitral flow velocity. The Valsalva maneuver typically induces a progressive decrease of E velocity. Measurements were obtained when the decrease in E velocity was maximum, and the Valsalva maneuver was considered valid only if there was >10% decrease of E velocity. In the case of an unsatisfactory recording, the patient was further instructed and asked to repeat the maneuver with a more shallow inspiration. A successful study of the transmitral flow velocity profile was possible in all patients but continuous-wave Doppler recordings of isovolumic relaxation time were unobtainable at rest or during Valsalva in 23 patients.

The patients were divided into 2 groups: group 1 consisted of 28 patients with normal results during exercise thallium study and no evidence of heart disease or hypertension; all had been referred for evaluation of atypical chest pain. Group 2 consisted of 94 patients with a positive result for ischemia on thallium stress testing (n = 48) or other evidences of disease such as: coronary artery disease on angiography (n = 19), previous myocardial infarction (n = 19), and hypertension (blood pressure >160/95 mm Hg on >3 separate occasions, n = 8). Continuous variables are expressed as mean ± 1 standard deviation. Statistical comparisons were performed using either the Student *t* test for comparisons between groups or the paired *t* test to evaluate differences in measurements before and after the Valsalva maneuver.

RESULTS

Table I lists the baseline measurements for the 2 groups of patients. Subjects without evidence of coronary disease or hypertension (group 1) had Doppler

measurements comparable to previously reported normal values. Significant differences observed in group 2 compared with group 1 were a slightly older age, a slightly higher A velocity, a lower E/A ratio, and a longer isovolumic relaxation time. The E/A ratio was ≥ 1.0 in all patients in group 1 and in 65 patients (69%) in group 2.

Changes observed during Valsalva are listed in Table II. Both groups had similar increases in heart rate and similar decreases in E velocity (-28 vs -32% , $p =$ not significant) but E/A ratio decreased significantly only in group 2 owing to a lesser decrease of A velocity in this group (-22 vs -8% , $p < 0.001$). On an individual basis, E/A ratio was ≥ 1.0 both before and during Valsalva (Figure 1) in all patients except 1 in group 1 (E/A during Valsalva = 0.96), whereas in group 2, 32 patients had E/A ≥ 1.0 at rest and during Valsalva, 33 patients had E/A ≥ 1.0 at rest but < 1.0 during Valsalva (Figure 2) and 29 patients had E/A < 1.0 both at rest and during Valsalva. In patients with E/A ≥ 1.0 at rest becoming < 1.0 during Valsalva, E velocity decreased to a greater extent than in group 1 patients during Valsalva (-37 vs -28% , $p < 0.001$), whereas A velocity actually increased instead of decreasing ($+10$ vs -22% , $p < 0.001$). Assuming that

E/A < 1.0 is a marker of abnormal diastolic function and using group 1 as controls, prevalence, specificity and positive predictive value of E/A < 1.0 in group 2 were 31, 100 and 100% at rest and 66, 96 and 98% during Valsalva (Figure 3). The correct classification of patients in groups 1 and 2 on the basis of E/A < 1.0 was 47% at rest and 73% during Valsalva. No significant differences in prevalence of E/A ratio < 1.0 was observed between patients with positive results during thallium study and those with other evidence of disease.

DISCUSSION

There is no gold standard for detecting LV diastolic function abnormalities, and the transmitral Doppler flow velocity profile is known to be influenced by factors such as age, heart rate and ventricular loading conditions.² For these reasons, we elected to evaluate the response of the Doppler indexes of diastolic function to changes in ventricular loading conditions in a large group of unselected patients, some of whom would likely be without evidence of heart disease and others with disease known to be associated with diastolic function abnormalities. We hypothesized that in patients with normal LV relaxation and normal left atrial pressure, a reduction in venous return would result in an overall

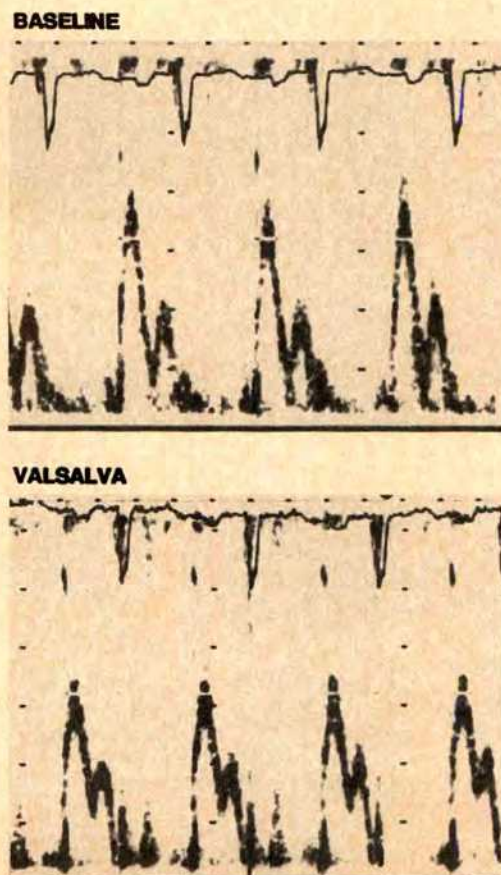


FIGURE 1. Transmitral flow velocity profile at rest and during Valsalva in a patient without evidence of disease. During Valsalva, E and A velocities decrease and E/A ratio remains > 1.0 .

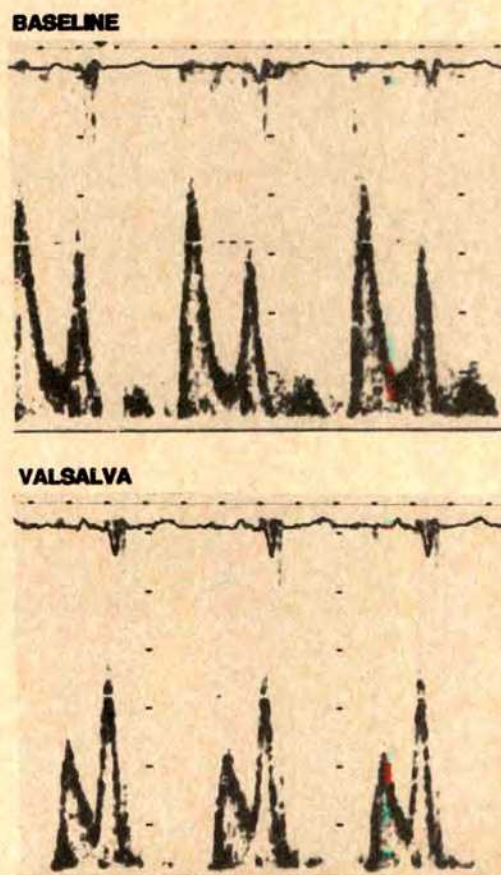


FIGURE 2. Transmitral flow velocity profile at rest and during Valsalva in patient with coronary artery disease. During Valsalva, E velocity decreases but A velocity increases, resulting in marked decrease of E/A ratio < 1.0 .

decrease of LV filling velocities without significant change in E/A ratio such as previously described in acute animal studies.⁷ In patients with abnormal relaxation and high left atrial pressures, a decrease of venous return would produce a reduction in initial (E) filling velocity. This could occur without a corresponding decrease in A velocity, given that early left atrial emptying is still abnormal and that with a lower pressure regimen the emptying due to atrial contraction may actually tend to increase instead of decrease.⁶ In such case, the E/A ratio would decrease and this could help differentiate between normal and so-called "pseudo-normal"⁴ transmitral Doppler flow velocity profiles. The Valsalva maneuver was chosen as the technique for reduction of atrial pressures because it is rapid, simple, noninvasive and easy to apply clinically.⁸ As expected, it produced a slight increase in heart rate and a decrease in E velocity, reflecting a decrease in the early diastolic gradient between left atrium and left ventricle due to a decrease in venous return. This reduction in E velocity, which was $\geq 10\%$ in all patients, can be used to verify that the Valsalva maneuver is properly performed. However, a change in position of the Doppler sample volume may artifactually reduce the E velocity as well as the E/A ratio, and it is therefore important to recheck the position of the sample volume before performing measurements.

The patients in group 1 had no evidence of heart disease and were used as controls. The Valsalva maneuver in this group produced relatively similar extents of decreased E and A velocities (28 and 22%, respectively) and, as hypothesized, there was little change in E/A ratio, which remained ≥ 1.0 in all but 1 patient. Choong et al.³ observed decreases in E/A ratio < 1.0 during nitroglycerin administration and stated that a reduction in filling pressures could "mimic" LV diastolic function abnormalities. However, 10 of their 11 patients had evidence of coronary artery disease or previous myocardial infarction. Stoddard et al.⁵ also reached

similar conclusions, but their measurements were obtained at the level of the mitral anulus rather than at the tips of the mitral valve, and the average E/A ratio in their group was < 1.0 both before and during nitroglycerin infusion. More recently, Lee et al.⁹ obtained measurements at the tips of the mitral valve in 10 normal subjects and observed a significant decrease in E velocity but no significant decrease in E/A ratio after nitroglycerin infusion, consistent with the results of the present study. Our results as well as those of Lee et al.⁹ suggest that if measurements are taken at the tips of the mitral valve, there is little chance of "mimicking" of diastolic function abnormalities by reducing pulmonary venous return in normal patients.

There clearly were 3 types of responses to Valsalva in our group 2 patients. Because there was only a slight difference in age between groups and heart rates were comparable, these different types of responses to Valsalva are likely related to the underlying state of relaxation and to ventricular loading conditions. The response in patients with E/A ≥ 1.0 at rest and < 1.0 during Valsalva is consistent with previous descriptions of a "pseudonormal" pattern,⁴ i.e., the underlying state of relaxation is abnormal but masked by increased left atrial pressures. The fact that the A velocity increased rather than decreased in these patients also confirms that this response is clearly different from that observed in other subgroups as well as in normal subjects. As previously suggested,⁴ this pattern may represent a more advanced stage of disease given that it reflects both an abnormal pattern of relaxation and higher left atrial pressures. On the other hand, it cannot be excluded that in some patients with heart disease and E/A ≥ 1.0 at rest and during Valsalva, the decrease in atrial pressures produced by Valsalva was not sufficient enough to unmask an underlying relaxation abnormality, particularly if A velocity increased instead of decreased, as was the case in 3 patients (9%) with this type of response.

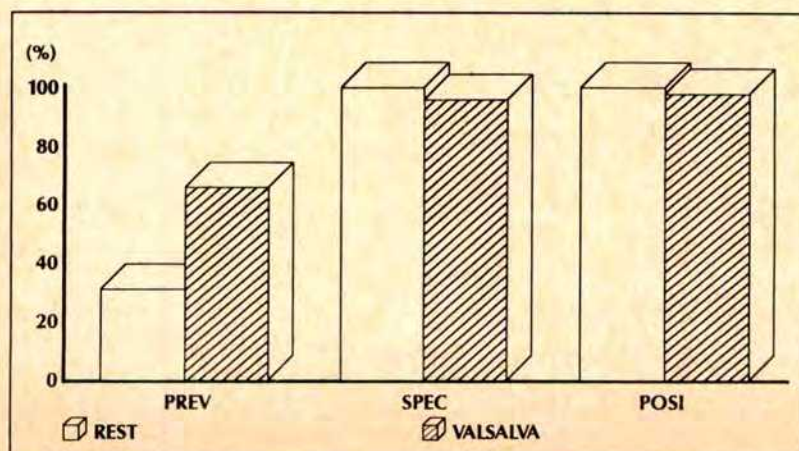


FIGURE 3. Prevalence (PREV), specificity (SPEC) and positive (POSI) predictive value of E/A < 1.0 at rest and during Valsalva in 94 patients with evidence of coronary artery disease or hypertension.

The main limitation of this study is that there was no mean of truly verifying underlying diastolic function. Nonetheless, the results clearly indicate that the Valsalva maneuver greatly enhances the detection of diastolic function abnormalities by Doppler echocardiography. Moreover, it is simple, rapid, easy to apply and can thus be performed on a routine basis.

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Electrocardiographic Correlates of Reperfusion Status After Thrombolysis: Is the "Incomplete" or "Interrupted" Infarction a Non-Q-Wave Infarction?

William E. Boden, MD

It is now generally accepted that non-Q-wave acute myocardial infarction (AMI) represents an aborted Q-wave infarction that culminates in an "incomplete" necrotic event with some degree of subepicardial salvage.¹⁻³ The precise pathogenesis of non-Q-wave AMI remains unclear. One of many proposed mechanisms which seems particularly attractive is that early spontaneous reperfusion of a total thrombotic coronary occlusion occurs during the early course of non-Q-wave AMI, resulting in an "altered reflow" phenomenon. Another possible pathogenetic mechanism is that the presence of focal vasospasm superimposed on a severely stenotic infarct-related coronary artery abates abruptly, resulting in partial restoration of anterograde coronary blood flow. In either case, altered early reflow would likely be a consequence of nonsustained coronary occlusion.

Somewhat analogous to "naturally occurring" non-Q-wave AMI is the incomplete infarction that results after acute thrombolytic therapy administered for evolving AMI. Successful reperfusion with intravenous thrombolytic therapy has now been clearly established to decrease mortality, promote myocardial salvage and enhance left ventricular function in selected patients with evolving AMI.⁴⁻⁸ The early administration of these agents produces partial recanalization of a total, or subtotal, thrombotic coronary occlusion, which then culminates presumably in an aborted or interrupted infarction. The net effect of such therapy is a salutary reduction in the magnitude of myocardial necrosis in patients whose AMI was destined to be more extensive (and presumably transmural) in the absence of early coronary reperfusion. There are several observations that support altered early reflow in naturally occurring non-Q-wave AMI (Table I). Similarly, those features of incomplete infarction that are shared by non-Q-wave

AMI and the reperfused AMI after thrombolysis are listed in Table II.

The pathogenetic and clinical features that naturally occurring non-Q-wave AMI and the pharmacologically reperfused AMI share are both intuitive and compelling; therefore, it is tempting to postulate a conceptual link between these 2 types of infarction as a singular manifestation of an incomplete or interrupted infarction. Figure 1 is a proposed schema of the characteristics and outcome after AMI—namely, the consequences of Q-wave and non-Q-wave AMI untreated with thrombolytic therapy, contrasted with that of AMI treated acutely with thrombolytic therapy. In many instances, it is difficult (if not impossible) to assess accurately the specific infarct subtype (Q-wave vs non-Q-wave) after the patient's admission to the hospital. In the absence of thrombolysis, some patients with acute ST-segment elevation will rapidly develop Q waves, whereas others will evolve Q waves over the course of days.⁹ Still others will not develop Q waves at all, presumably indicative of non-Q-wave AMI with spontaneous coronary reperfusion.

Thus, it may be more appropriate to regard AMI as "electrocardiographically undifferentiated" during the first several hours after the index event (Figure 1), until such time as the electrocardiogram (ECG) evolves over a sufficient time period (generally 24 to 48 hours).⁹ However, from a practical standpoint, this is not a feasible strategy, because decisions regarding the use of acute thrombolytic therapy must be made emergently, before the ECG can serve to guide therapy.

Nevertheless, the ECG is not totally useless as a diagnostic tool for evolving AMI, and general guidelines permit important clinical distinctions. For example, patients who present with prolonged chest pain in the context of ≥ 0.2 mV ST-segment elevation in ≥ 2 contiguous electrocardiographic leads are likely to evolve a Q-wave AMI in the absence of thrombolytic therapy.^{10,11} More diminutive amounts (0.1 to 0.2 mV) of ST-segment elevation, however, may be encountered in either evolving Q-wave or non-Q-wave AMI.¹²⁻¹⁴ Pooled data from 3 published trials of non-Q-wave AMI indicate that 43% of such patients exhibit early

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TABLE I Observations Supporting Altered Early Reflow in Naturally Occurring Non-Q-Wave Acute Myocardial Infarction

Early electrocardiographic evidence of acute ST-segment elevation in 40 to 45% of patients
Early time-to-peak creatine kinase release
Histologic evidence of contraction band necrosis
Low incidence of postmortem intracoronary thrombi
High incidence of patent infarct-related coronary arteries at necropsy
High incidence of incomplete coronary occlusion at cardiac catheterization within first 24 to 48 hours after AMI
Thallium scintigraphic evidence of increased residual myocardial ischemia in left ventricular segments subtending the infarct-related coronary artery
Lack of circadian rhythm or diurnal variation in onset of non-Q-wave AMI
Dynamic changes in coronary vasomotor tone in the pathogenesis of reinfarction and recurrent ischemic events

AMI = acute myocardial infarction.

TABLE II Features of Incomplete Infarction Shared by Non-Q-Wave Acute Myocardial Infarction and Reperfused Acute Myocardial Infarction After Thrombolysis

Subtotal coronary occlusion
Early creatine kinase wash-out
Preservation of global and regional left ventricular function
High incidence of reinfarction and postinfarction angina
High incidence of residual myocardial ischemia during noninvasive testing

ST-segment elevation on admission to the hospital.¹⁵ Accordingly, acute ST-segment shifts may be a poor predictor of subsequent Q-wave evolution.¹³ The implications of this observation are that patients with non-Q-wave AMI, who appear to have a propensity to achieve reperfusion of their occluded infarct-related coronary arteries spontaneously, may be indistinguishable from patients with completely occluded coronary arteries who exhibit successful reperfusion after thrombolytic therapy. Thus, if a patient with evolving non-Q-wave AMI were to receive thrombolytic therapy, it might be difficult to interpret whether angiographically documented recanalization was a direct consequence of therapeutic intervention or a manifestation of spontaneous reperfusion.

Not only are ST-segment shifts unreliable predictors of subsequent Q-wave development after infarction,^{13,15} but the subsequent development (or lack thereof) of Q waves may be exceedingly difficult to interpret in the context of thrombolytic therapy. With the exception of performing diagnostic coronary angiography to verify infarct vessel patency after thrombolysis, there are obvious inherent problems in assessing reperfusion status clinically or electrocardiographically. As mentioned, it is now becoming commonplace to refer to AMI treated with thrombolysis as an interrupted or incomplete infarction. Accordingly, there is legitimate uncertainty as to whether it is, in fact, appropriate to classify reperfused myocardial infarctions according to the commonly used dichotomous electrocardiographic designation of Q-wave or non-Q-wave AMI.

In this issue of *The American Journal of Cardiology*, Chouhan et al¹⁶ describe the clinical and electrocardiographic features of 75 consecutive patients who presented initially with chest pain and anterior (ECG leads I, aVL and V₁-V₆) ST-segment elevation, and who were treated with intravenous streptokinase within 3 hours of presentation. The purpose of their analysis was to assess the incidence of Q-wave development af-

ter reperfusion, and to contrast the clinical, angiographic, enzymatic and postinfarction ischemic complications with those of patients who had successful reperfusion after intravenous streptokinase, but did not evolve new Q-waves. They observed that, on the basis of serial ECG, 57% of treated patients developed Q-wave AMI after thrombolysis, compared with 43% of patients in whom non-Q-wave infarction persisted after intravenous streptokinase. Although the subgroup of AMI patients with continuing non-Q-wave infarction had a significantly lower left ventricular end-diastolic pressure, a lower peak creatine kinase level and a higher left ventricular ejection fraction than patients who developed Q-waves after thrombolysis, there were no significant between-group differences in infarct vessel patency during coronary angiography obtained 5 ± 2 days after AMI (non-Q-wave AMI group 85% vs Q-wave AMI

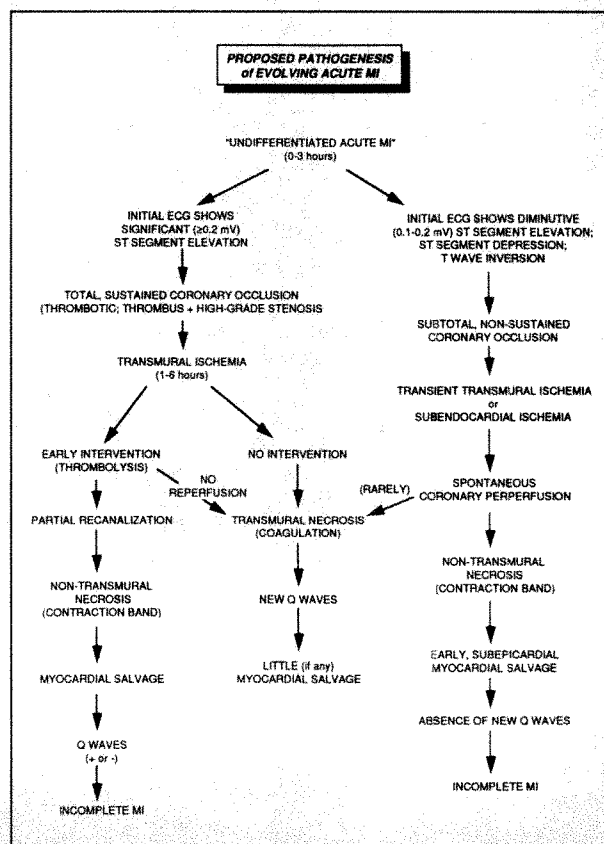


FIGURE 1. Proposed pathogenesis of evolving acute myocardial infarction (MI).

TABLE III Electrocardiographic Patterns of Q-Wave Development

Reference	Method	Group	n	Q Wave			
				Before Therapy	Early After Therapy	One Day After Therapy	Late After Therapy
Blanke et al ²⁴	nQ*	Control	22	1.9	3.0	3.2	3.2
		SK	15	1.7	2.5	2.4†	1.8†
Anderson et al ²⁵	nQ‡	Control	26	1.8	2.4	3.6	3.8
		SK	24	1.0	1.4†	2.5†	2.0§
Timmis et al ²⁷	Single Q	Not reperfused	8	0.21	—	0.33	—
		Reperfused	27	0.24	—	0.31	—
TIMI ²⁸	Mean Q¶	Not reperfused	30	0.23	—	—	0.65
		Reperfused	36	0.23	—	—	0.62
		Incomplete	16	0.13	—	—	0.23§

*In leads V₁ to V₆.

†p < 0.05 vs control subjects; §p < 0.01 vs control subjects or not reperfused.

‡In all infarct leads.

||In lead with greatest pretherapy ST elevation in mV.

¶Mean of 2 contiguous leads with greatest pretherapy ST elevation in mV.

Incomplete = initial incomplete occlusion; nQ = non-Q wave; Q = Q wave; SK = streptokinase; TIMI = Thrombolysis in Myocardial Infarction trial.

group 72%; α = not significant) or in the incidence of recurrent postinfarction angina, reinfarction or death.¹⁶

The incidence of so-called non-Q-wave AMI after successful reperfusion with intravenous streptokinase (43%) is virtually identical to that of naturally occurring non-Q-wave AMI (range 40 to 45%).¹⁷⁻¹⁹ Such observations emphasize how commonplace non-Q-wave AMI has become over the last 2 decades,^{20,21} and underscore the extent to which thrombolytic therapy may be contributing to the expanding pool of patients with incomplete infarction.

Similar findings have been reported in a recent publication in this journal by Eisenberg and et al.²² They showed that 70% of 201 patients with evolving AMI treated with recombinant tissue plasminogen activator developed Q waves after 3 hours of lytic therapy, whereas the remaining 30% did not. These latter patients were characterized by a significantly smaller mean peak creatine kinase release, higher radionuclide ejection fraction, lower incidence of congestive heart failure at discharge and lower in-hospital mortality findings that were remarkably similar to those patients with naturally occurring non-Q-wave AMI. Thus, in patients who received thrombolytic therapy, hospital morbidity and mortality rates were higher for those patients who developed Q-wave AMI than for those who continued to have non-Q-wave (or exhibited delayed Q-wave) AMI.²²

Because the appearance of Q-wave AMI depends on the amount and site of myocardial necrosis, it is possible that, as in patients with a non-Q-wave AMI in whom the amount of myocardium destroyed is presumably insufficient for abnormal Q waves to evolve, patients who fail to develop Q waves after thrombolysis likewise appear to have smaller infarcts. Therefore, it would appear that successful intervention with thrombolytic therapy has curtailed or attenuated the process of myocardial necrosis, resulting in either delayed or

absent Q-wave evolution. Such electrocardiographic findings may be distinctly prevalent among patients with AMI who are treated with thrombolytic therapy and who, presumably, display a higher incidence of incomplete infarcts.

However, it is important to emphasize that the electrocardiographic distinction between Q-wave and non-Q-wave AMI—and between transmural and nontransmural necrosis—is imprecise with or without acute thrombolytic therapy administration. Any binary classification system that fails to take into account the heterogeneous manifestations of AMI seems doomed to oversimplification and potential misinterpretation.

In a thorough review of the ECG in patients undergoing thrombolysis for AMI, Bren et al²³ assessed the utility of the 12-lead scalar ECG in identifying reperfusion status. Six studies compared indexes of ST-segment elevation between groups who received thrombolytic therapy and control (or nonreperfused) groups, and there was marked heterogeneity in the magnitude of ST-segment elevation early after therapy among the studies.²⁴⁻²⁹ With the use of a variety of electrocardiographic markers (sigma, or summed, ST-segment elevation,²⁴⁻²⁶ maximal ST-segment deviation in a single electrocardiographic lead^{27,28} or continuous 12-lead electrocardiographic recording²⁹), 4 studies showed less ST-segment elevation after thrombolytic therapy^{24-26,29} compared with control subjects, whereas 2 did not.^{27,28} Though it would seem reasonable to conclude that when large groups of patients are analyzed, the magnitude of ST-segment decline in patients with successful reperfusion is greater than in those without reperfusion or in control subjects, these differences are for the most part small, and therefore are not likely to be of benefit in predicting the angiographic result in an individual patient.²³

Four of these studies have evaluated the electrocardiographic evolution of AMI pattern after thrombolysis

based on depth of Q waves in infarct leads (Table III).^{24,25,27,28} As with ST-segment analysis, results are conflicting, but general conclusions can be drawn: In all, 204 patients underwent serial electrocardiographic assessments before therapy, and early after and late after therapy.²³ Two studies^{24,25} showed a significant reduction in the number of Q waves 1 day after therapy and late after therapy with streptokinase compared with control subjects, 1 study showed no change early after therapy,²⁷ and 1 study showed a significant decrease in mean Q-wave development late after therapy only in patients with incomplete coronary occlusion.²⁸ However, the absolute magnitude of Q-wave differences tends to be small and standard deviations are large.²³

In summary, it appears that the ECG is too blunt an instrument to dichotomize with precision the state of reperfusion after thrombolysis. Clearly, the ECG is a helpful but imperfect tool for use in the management of patients with AMI who have received thrombolytic therapy. The ECG does not appear to be helpful in identifying patients with an initially incomplete coronary occlusion who may not require thrombolytic therapy. Although the ECG can demonstrate successful reperfusion when applied to large groups of patients, the small group differences and wide variability of responses make its value in the individual patient minimal.²³ The same appears to be true for the recognition of altered patterns of electrocardiographic Q-wave evolution as a result of thrombolytic therapy, although Chouhan et al¹⁶ demonstrated distinct clinical outcome differences in patients receiving streptokinase who do and do not evolve Q-waves after thrombolysis.

Hopefully, newer technologies such as spin-echo magnetic resonance imaging³⁰⁻³² or cinemagnetic resonance imaging³³⁻³⁴ may overcome some of these shortcomings and limitations of standard electrocardiographic assessments. Future clinical investigation may prove to be effective in evaluating and detecting myocardial salvage after mechanical and pharmacologic interventions.

Finally, the therapeutic implications of the "incomplete infarction" warrant comment. The optimal adjunctive therapy after thrombolytic therapy remains to be elucidated. The American College of Cardiology/American Heart Association Joint Task Force³⁵ recommendations on therapy after AMI indicated that early intravenous metoprolol was a class I indication for selected patients after thrombolysis, but did not recommend routine β -blocker administration for all patients. Similarly, oral β blockers and calcium antagonists were recommended as class IIA (possibly effective) agents for routine prophylaxis.³⁵

Within the class of calcium antagonists, 2 studies have shown that diltiazem has salutary effects on both

short- and long-term outcome in patients with non-Q-wave AMI.³⁶⁻³⁸ In the Diltiazem Reinfarction Study,³⁶ diltiazem was shown to reduce the in-hospital reinfarction rate by 51% in non-Q-wave AMI compared with placebo. There was a similar 49% reduction in medically refractory angina, but overall, there were no differences in 2-week mortality, probably because of the short-term study design and the overall low (3.5%) 2-week mortality rate.

In the Multicenter Diltiazem Post-Infarction Trial,³⁷ there was a 40% reduction in 1-year cardiac event rate (cardiac death or nonfatal AMI) in 634 non-Q-wave AMI patients who were randomly assigned to long-term diltiazem treatment. Over the entire 52-month follow-up, the cardiac event rate was significantly reduced by 34% in the diltiazem group (Cox hazard ratio/95% confidence interval = 0.66 [0.44 to 0.98]) compared with placebo.

In a more recent electrocardiographic post-hoc analysis, diltiazem was shown to be especially beneficial in patients with a first non-Q-wave AMI.³⁸ In these patients, diltiazem administration was associated with a 48% reduction in long-term (mean \pm standard deviation 25 \pm 8 months) cardiac event rate (Cox hazard ratio/95% confidence interval = 0.48 [0.26 to 0.88]) compared with placebo.³⁸

In summary, given the similarities between naturally occurring non-Q-wave AMI and AMI "interrupted" by acute thrombolytic therapy, there appears to be a rational basis to advocate diltiazem as an appropriate adjunctive therapy for the incomplete infarction. This certainly seems in keeping with published American College of Cardiology/American Heart Association Joint Task Force guidelines to regard diltiazem as "possibly effective" for use in patients after non-Q-wave AMI and as an adjunctive oral therapy after thrombolytic therapy.³⁵

However, until there are prospectively acquired data to further clarify the role of calcium antagonists versus β -blockers after thrombolysis, it seems prudent to emphasize that the decision to use different classes of antiischemic drugs as adjuvant therapy for patients who have received thrombolytic therapy should remain empirical and individualized.

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Spasm and Arterial Injury

Jay Hollman, MD, and Curtis R. Partington, PhD, MD

Fischell and his group at Stanford have studied the relation between arterial injury and acute vascular spasm through clinical observations^{1,2} and more basic science studies.^{3,4} In this edition of *The American Journal of Cardiology*, they contrast eccentric and concentric lesions and demonstrate that both types of lesions are equally susceptible to coronary spasm after balloon injury.¹

Coronary spasm at the angioplasty site has been associated with recurrent stenosis since the early days of coronary angioplasty.⁵ These observations formed the rationale for several clinical studies of spasm; the most complete one, by Bertrand et al,⁶ demonstrated that ergonovine-induced coronary artery vasoreactivity at the percutaneous transluminal coronary angioplasty (PTCA) site was associated with more than doubling of the recurrent stenosis rate. Despite this firm correlation, several randomized trials of calcium antagonists given after PTCA have failed to demonstrate a decrease in recurrent stenosis, either because these drugs are not powerful enough to change local coronary tone or because the spasm is merely a marker for a lesion likely to recur, i.e., spasm is associated with recurrence but does not cause it. This "chronic" spasm, however, is not the phenomenon that the Stanford group is studying. The Stanford group is studying acute changes in arterial tone after vascular injury. This phenomenon is not related to recurrent stenosis but is probably related to acute occlusion (Table I).

Acute spasm is nearly universal at 30 minutes after arterial injury² unless aggressive measures are taken to prevent it (such as intravenous nitroglycerin and calcium antagonists). Fortunately, the spasm is occlusive only in about 2 to 4% of patients.⁷ Arterial injury by whatever mechanism induces coronary spasm. Persons who attempt suicide by slashing their wrists are often saved by spasm in their radial artery. A resistant form of arterial spasm can occur after the arterial injury that results from bypass surgery. Those performing renal artery angioplasty have noted clinically significant spasm in 26% of patients.⁸ Cerebral aneurysms frequently induce distal cerebral arterial spasm with disastrous consequences. The presence of blood breakdown products in the subarachnoid space after subarachnoid hemor-

rhage induces arterial spasm which is very difficult to alleviate. This frequently leads to cerebral infarction.

Mechanism of acute arterial spasm: Regardless of the exact mediators involved, it is clear that this reflex could have a protective influence for total body survival. Arterial spasm by an injured artery should reduce hemorrhage. The artery cannot differentiate between a "therapeutic injury" induced by a balloon, and a surgeon's knife or a laser from a harmful injury from a bullet or other penetrating injury. In vitro studies have demonstrated that endothelium is required for this increase in vascular tone.³ The gradual loss of endothelium over the first 24 hours after balloon arterial injury might well explain the exponential decline in incidence of severe arterial spasm (acute occlusion) after coronary angioplasty. This vasoconstriction can occur in the absence of blood interaction, implying that the endothelium-derived cyclooxygenase products might be the responsible messengers. The fact that antiplatelet drugs help prevent complications of acute occlusion⁹ may mean that platelet-derived cyclooxygenase products act in synergism with endothelium products to produce spasm.

Neurologists and neurosurgeons studying the phenomenon of cerebral spasm distal to a leaking cerebral aneurysm have postulated adventitial irritation from hemorrhage as a mechanism.¹⁰ Intradural arteries are extremely sensitive to initiation of spasm through both endothelium- and adventitial-mediated processes. Adventitial-mediated arterial spasm occurs in response to irritants in the subarachnoid space (blood degradation products after subarachnoid hemorrhage, leukocyte-derived products in meningitis) and is related to external irritation of the cerebral artery.

This observation is in exact agreement with the view that large intimal tears are more frequently associated with acute occlusion after coronary angioplasty.⁷ In such cases the adventitia is irritated from direct contact through the intima media split. External hemorrhage can be seen over the angioplasty site at the time of bypass surgery (Figure 1). One common thread is seen through these mechanisms: local injury or vessel irritation, internal or external, results in focal spasm at the injury site.

Practical points to consider regarding arterial spasm: First, one should recognize that this entity exists. When lesions change from 10% residual stenosis 5 minutes after PTCA to 30% narrowing at 30 minutes, clinicians performing angioplasty should not become

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TABLE I Two Types of Spasm After PTCA

	Acute Spasm	Chronic Spasm
Time of onset after PTCA	0–36 hours	Days to months
Incidence	Nearly 100% to some degree	25–30% of patients
Relation to recurrence	No relation	Presence associated with 2× recurrence rate

PTCA = percutaneous transluminal coronary angioplasty.

too alarming. Often when multivessel PTCA is performed the first lesion will be 10 to 20% narrower on angiography after the second lesion is done. In general, if the first lesion is still <50% narrowed, the lesion should be treated with intraarterial nitrates but not repeat angioplasty.

Second, it is advisable to avoid hypotension. Pressor agents can be given but in gentle doses. Dopamine is generally limited to 10 $\mu\text{g/kg/min}$. The most effective therapy for hypotension is intraaortic balloon pumping, which raises diastolic (coronary perfusion) pressure. Intravenous fluids and volume expansion should be the first measures undertaken.

Third, antiplatelet agents and anticoagulation reduce the risk of acute occlusion. It has been helpful to us to monitor anticoagulation using activated clotting times. In general, ACT >300 seconds is verified before performing arterial injury.

Fourth, pharmacologic measures are generally effective only if given early. As the Stanford group has demonstrated, larger doses of nitroglycerin are often necessary (they use 300 μg , intracoronary). Failure to respond to intracoronary nitroglycerin does not mean that the vessel is not closed because of spasm. Intraarterial papaverine is now used in many academic laborato-

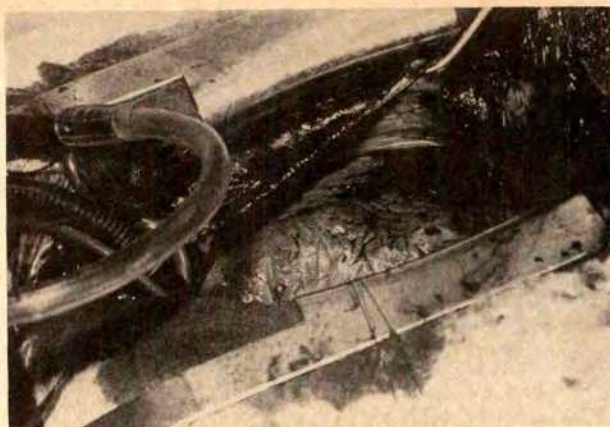


FIGURE 1. Hemorrhage over the right coronary artery external to the angioplasty site.

ries to measure coronary flow reserve. This has been useful for relieving refractory spasm.

When spasm progresses to total occlusion, pharmacologic measures are often not effective and dilation is needed to reopen the vessel. In fact, dilation is being performed clinically in humans to relieve the spasm that occurs distal after subarachnoid hemorrhage (Figure 2). Such heroic brain-saving intervention must be performed quickly, and frequently has striking results.

Speed is of the utmost importance in treating acute occlusion after PTCA. The earlier the vessel is reopened, the more likely the patient will avoid myocardial damage and the more likely the vessel will remain patent. Interventional laboratories need a mechanism to

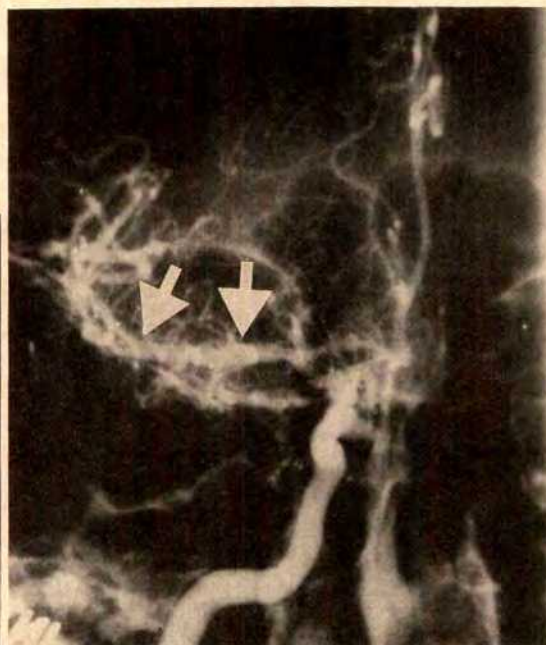


FIGURE 2. Left, frontal view from a right internal carotid arteriogram of a patient who was acutely hemiplegic 4 days after subarachnoid hemorrhage, showing right spasm of the M-1 segment of the middle cerebral artery (arrows). Right, similar view recorded after balloon angioplasty of the M-1 segment, showing a widely patent middle cerebral artery (arrows). The patient's hemiplegia improved markedly immediately on dilation. The appearance of the middle cerebral artery was identical 2 weeks later: a widely patent middle cerebral artery and no residual hemiplegia.

quickly bring the patient back to the laboratory if the patient develops significant spasm. The use of arterial stent¹¹ and thermal catheters¹² for acute occlusion shows promise, but are necessary only when PTCA is not successful or when an arterial dissection significantly compromises arterial flow.

Taken together, the research of the Stanford group and the clinical observations of acute occlusion supply useful information that can aid in patient care. Arterial injury makes a vessel less stable and susceptible to vasoconstriction. This instability persists for 24 to 36 hours until endothelium is denuded and perhaps the initial platelet interaction with the newly exposed surface is complete. Initial vessel instability is not related to chronic arterial spasm, but occurs to some degree in every patient and is a part of the initial phase of arterial healing.

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Underutilization of Thrombolytic Therapy in Eligible Women with Acute Myocardial Infarction

Charles Maynard, PhD, Ralph Althouse, MD, MPH, Manuel Cerqueira, MD, Michele Olsufka, RN, and J. Ward Kennedy, MD

New methods for the management of coronary artery disease are almost always evaluated in male patients or in groups of patients who are predominantly male.¹ This bias is in part due to the fact that men develop coronary artery disease more frequently and at an earlier age than do women.² This problem is compounded by the usual practice of excluding elderly patients from therapeutic trials. Most trials of thrombolytic therapy for acute myocardial infarction (AMI) have an upper age limit of 70 or 75 years, as was the case in our own trials.³ Because thrombolytic therapy has been largely evaluated in men, we have been concerned that once this therapy was demonstrated to be effective, it might be preferentially applied. In this analysis, we attempt to specify the role of gender in the eligibility for and use of thrombolytic therapy.

As part of the Western Washington emergency department recombinant tissue plasminogen activator trial, all patients with documented AMI in 8 hospitals in the Seattle-Tacoma metropolitan area were identified.³ From the medical record, patient age, sex, inclusion and exclusion criteria for the trial, and the use of thrombolytic therapy in general were determined. Information on cardiac catheterization, coronary angioplasty and coronary artery surgery was also col-

lected. Exclusion criteria, including age >75 years, time from symptom onset to hospital arrival >6 hours, nondiagnostic electrocardiographic changes, and medical contraindications to thrombolytic therapy were reviewed in detail as was vital status at the time of hospital discharge. We also attempted to determine from the medical record why eligible patients did not receive thrombolytic therapy. In all, 1,028 patients with AMI, including 160 enrolled in the clinical trial, comprised the population for this analysis.

Between January 1987 and January 1988, 675 (66%) men and 353 (34%) women with AMI were admitted to the 8 participating hospitals. A higher proportion of women were >75 years; women were also older than men (72 ± 9 vs 65 ± 12 years, $p < 0.0001$) (Table I). Of the 221 (21%) patients who were eligible for thrombolytic therapy, men were more often eligible than women. Men and women differed in the reasons for ineligibility (Table I). Multiple reasons for ineligibility were noted more often in women than in men (65 vs 55%, $p = 0.02$).

Eligible men received thrombolytic therapy as part of the clinical trial more often (Table I); i.e., only 55% of 55 eligible women received the drug, whereas 78% of 166 eligible men did. It was difficult to determine from the medical record why eligible patients did not receive thrombolytic therapy, since this information was unknown for 41% of these 61 patients. Similar proportions of men and women either refused or were not offered thrombolytic therapy by their physicians. An additional 3 men and 5 women, who were eligible, received thrombolytic therapy outside the trial. In addition, 9 men and 2 women, who were ineligible by study criteria, also had thrombolytic therapy.

The use of diagnostic and reperfusion procedures was also examined. Only 5 angioplasties and 4 surgical revascularizations were performed in the 265 pa-

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TABLE I Eligibility of Women and Men with Acute Myocardial Infarction for Thrombolytic Therapy

	Women (%) (n = 353)	Men (%) (n = 675)	All (%) (n = 1,078)	p Value
Age > 75 years	39	19	26	<0.0001
Nondiagnostic electrocardiogram	59	53	55	0.09
Presented > 6 hours	30	27	18	0.71
Medical contraindication	33	32	33	0.78
Eligible for thrombolytic therapy	16	25	22	0.0008
Eligible patients receiving thrombolytic therapy	55	78	72	0.0006
(no. of eligible pts.)	55	166	221	

TABLE II Procedures, Treatments and Hospital Mortality for Patients Aged ≤ 75 Years

Event	Women (%) (n = 353)	Men (%) (n = 548)	p Value
Cardiac catheterization	39	46	0.08
Thrombolytic therapy	17	26	0.01
Coronary angioplasty	9	8	0.46
Coronary artery surgery	11	13	0.53
Hospital death	10	11	0.89

tients aged >75 years. Only 1 patient >75 years was given thrombolytic therapy. Table II displays the use of these procedures in patients ≤75 years. Although a higher proportion of men underwent cardiac catheterization, the difference between men and women was not statistically significant. However, 26% of all men received thrombolytic therapy, whereas only 17% of all women did. Hospital mortality was similar in all men and women (13.3 vs 14.2%, $p = 0.88$) and in men and women aged >75 (25.2 vs 20.3%, $p = 0.34$). After adjustment for age, hospital mortality in men and women of all ages remained similar.

It is difficult to explain the underutilization of thrombolytic therapy in women. It is possible that eligible women were closer in age to the upper limit of 75 years and thus were considered ineligible. However, eligible men and women not treated within the trial had the same mean age of 62 years. It is also plausible that women were treated less aggressively by predominantly male cardiologists. This is unlikely, since similar proportions of men and women underwent cardiac catheterization, coronary angioplasty and bypass surgery. Of course, the differential use of thrombolytic therapy may have been due to chance or to confounding variables. This is a

possibility, since we are unaware of other studies that report the underutilization of thrombolytic therapy in women.^{4,5} However, databases of trials of thrombolytic therapy should be examined to determine if there are gender differences in the use of thrombolytic therapy. Nevertheless, in this study, women were more often ineligible for thrombolytic therapy and were less often treated with thrombolytic agents even though eligible for treatment.

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Effects of Luminal Eccentricity on Spontaneous Coronary Vasoconstriction After Successful Percutaneous Transluminal Coronary Angioplasty

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Over the past several years there has been increasing recognition that spontaneous coronary artery vasoconstriction, or spasm, can occur in the dilated coronary segment after percutaneous transluminal coronary angioplasty (PTCA). This vasoconstriction after PTCA has been quantitated in clinical studies,^{1,2} and has been well described in clinical series and in case reports.³⁻⁶ Although the etiology of vasoconstriction after PTCA is not fully understood, several mechanisms have been postulated, including the release of vasoactive substances from aggregating platelets at the site of endothelial injury and the release of endothelium-derived constricting factor(s) after balloon trauma.⁷ Coronary spasm has been demonstrated to be one possible mechanism of acute vessel closure after successful PTCA.^{5,6} Furthermore, clinical studies have suggested a significant correlation between spontaneous or provoked vasospasm

in the dilated coronary segment with increased restenosis rates after PTCA.⁸

It has been demonstrated that lesion eccentricity may be a risk factor for acute coronary closure after PTCA.⁹ The observations that eccentric lesions may have a greater potential for dynamic changes in caliber in response to vasoactive stimuli¹⁰ has led to speculation that vasospasm may be more pronounced after PTCA in eccentric compared with concentric lesions, leading to a greater incidence of acute closure, and possibly late restenosis.^{11,12} This study was designed to examine whether there is any relationship between angiographically determined lesion eccentricity and the severity of spontaneous vasoconstriction early after PTCA in the dilated coronary segment.

Sixteen patients scheduled for elective 1-vessel PTCA of focal stenoses were prospectively entered into the study after informed consent for both PTCA and the study was obtained. Three of these 16 patients had been entered into a previously reported study¹ of vasomotion after PTCA. Exclusion criteria included concurrent nitroglycerin therapy, recent myocardial infarction (<2 weeks), length of lesion to be dilated

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>10 mm, requirement for intracoronary nitroglycerin during PTCA, and technically inadequate coronary arteriography.

All patients took their usual oral medications including aspirin and calcium antagonists on the day of the procedure. Selective coronary arteriography of the vessel to be dilated was performed in multiple projections, including at least 1 pair of orthogonal views using Omnipaque® contrast at a cine rate of 30 frames per second.

Coronary angioplasty was performed using either an over-the-wire balloon catheter system (14 patients) or a fixed wire balloon catheter system (2 patients). Balloon sizes were chosen to approximate the diameter of the "normal" coronary segment adjacent to the segment to be dilated. At least 2 balloon inflations were performed in each case, with additional infla-

tions performed as needed until the coronary stenosis had been dilated adequately using angiographic or hemodynamic criteria, or both.

As soon as was feasible after the final balloon inflation (average 3 minutes; range 2 to 5 minutes), the balloon catheter and guidewire were withdrawn and selective coronary arteriography, in the previously selected projection was performed. This angiogram was designated "post-PTCA." The coronary guiding catheter was replaced with an 8Fr right or left coronary artery Judkins "marker" catheter, to be used as a reference for coronary quantitation. Coronary arteriograms (same projection) were repeated at 15 and 30 minutes after the final balloon inflation, and again 3 minutes after the administration of 300 µg of intracoronary nitroglycerin given immediately after the 30-minute angiogram (i.e., 33 minutes after the final

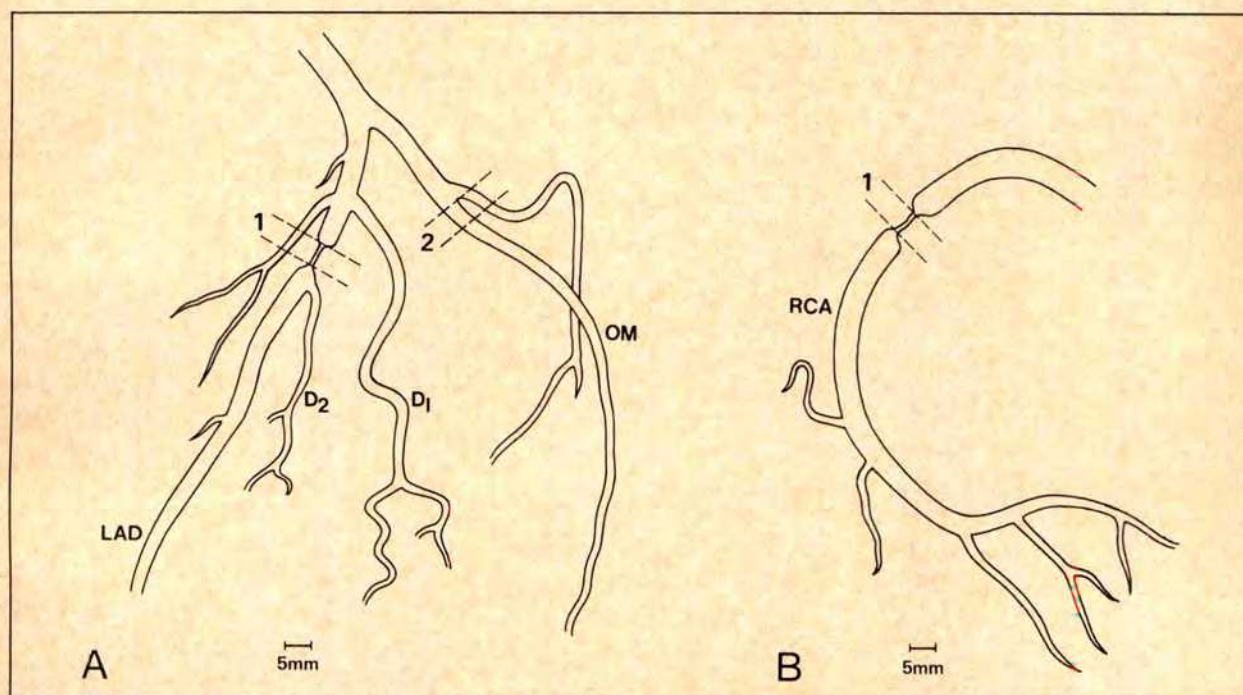


FIGURE 1. Diagram of 5-mm coronary artery segments analyzed by quantitative coronary arteriography in the left (panel A) and right (panel B) coronary arteries. Segment 1 (angioplasty segment) was defined as the 5-mm-long segment centered in the narrowest point of the coronary stenosis to be dilated; segment 2 (control segment, left coronary artery only) was defined as a segment in the left coronary artery not manipulated by the guidewire or balloon catheter. LAD = left anterior descending artery; OM = obtuse marginal branch; RCA = right coronary artery.

FIGURE 2. Definition of lesion eccentricity. A cineangiographic frame from the view showing the stenosis at its most severe narrowing and eccentric morphology is traced. A centerline is drawn for the normal adjacent lumen, and "b" is designated as the angiographic radius of the normal vessel. A second centerline is drawn for the stenotic (lesion) lumen, with "a" being the perpendicular distance from this centerline to the adjacent normal vessel wall. If the ratio a/b is ≤ 0.5 , the lesion is defined as eccentric. In this example $a/b = 0.43$.

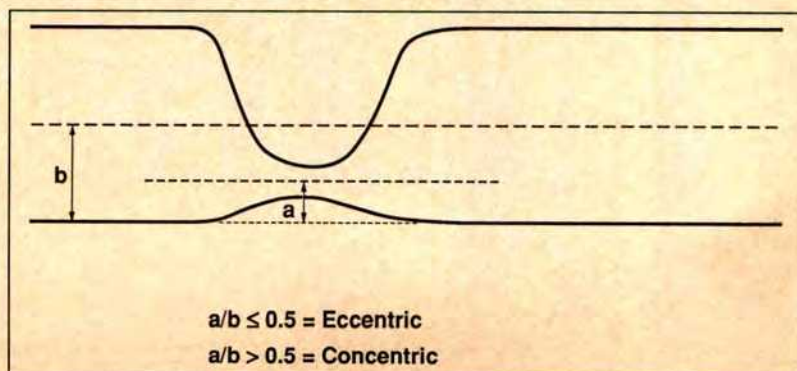


TABLE I Patient and Procedural Data

Pt. Group	Lesions	
	Concentric	Eccentric
No. of patients	8	8
Age (mean years)	61 ± 2	58 ± 3
Men/women	8/0	7/1
Coronary dilated	3 LAD, 3 Cx, 2 RCA	4 LAD, 2 Cx, 2 RCA
% stenosis	66 ± 3	71 ± 3
Lesion eccentricity (a/b)	0.81 ± 0.15	0.43 ± 0.08*
Lesion (min.) diameter (mm)	0.92 ± 0.09	0.83 ± 0.12
Final (min.) diameter (mm)	1.85 ± 0.21	2.02 ± 0.24
Balloon size (mean) (mm)	2.6	2.8
No. of inflations (mean)	3.6	4.0
Max. inflation pressure (mean atm)	7.1	7.2

*p < 0.01 for eccentric versus concentric lesion groups. Values are mean ± standard error of the mean. Cx = left circumflex coronary artery; LAD = left anterior descending coronary artery; Max. = maximal; min. = minimal; RCA = right coronary artery.

balloon inflation). All films were analyzed by quantitative arteriographic techniques as previously described.^{1,2} The resolution of this system has been demonstrated to be ± 0.06 mm.

Two coronary segments were analyzed in patients undergoing PTCA in the left coronary artery system, Figure 1A. For the 4 patients undergoing right coronary artery PTCA, only segment 1 was analyzed since there was no equivalent "Control" segment (Figure 1B).

One of the 2 designated film readers analyzed the mean and minimal segmental diameters in each of 3 consecutive end-diastolic frames for each 5-mm-long segment, at each time/condition. The final segmental vessel diameter (mean and minimum) at each time was defined as the mean of the 3 end-diastolic measurements.

TABLE II Coronary Artery Diameters (minimum in mm): Angioplasty Segment (segment 1)

Pt. No.	Pre-PTCA	Post-PTCA	15 Min	30 Min	After IC NTG
Patients with Concentric Lesion					
1	0.99	1.87	1.21	1.26	1.90
2	1.04	1.79	1.61	1.40	1.85
3	1.25	2.56	2.08	1.95	2.51
4	0.97	1.76	1.38	1.40	1.84
5	0.88	1.28	1.09	1.11	1.37
6	0.91	1.99	1.62	1.41	1.90
7	0.76	1.92	1.55	1.57	1.68
8	0.61	1.63	0.96	0.76	1.44
Patients with Eccentric Lesion					
1	0.77	2.20	1.73	1.51	2.26
2	1.01	1.73	1.30	1.24	1.80
3	1.18	2.02	1.30	1.48	2.35
4	0.74	2.62	1.94	2.07	2.56
5	0.80	2.14	1.83	1.62	2.07
6	0.52	2.13	1.59	1.57	2.41
7	1.12	2.21	1.58	1.37	1.81
8	0.53	1.07	0.91	0.81	1.07

After IC NTG = angiogram obtained 3 minutes after 300 µg of intracoronary nitroglycerin (33 minutes after final balloon inflation); Post-PTCA = angiogram obtained 2 to 5 minutes after final balloon inflation, guidewire removed; Pre-PTCA = angiography before crossing lesion; 15 Min = angiogram 15 minutes after final balloon inflation; 30 Min = angiogram 30 minutes after final inflation.

For the purposes of defining lesion eccentricity, a coronary lesion was defined as eccentric if the luminal center line at the narrowest point of the stenosis was in the outer 25% of the adjacent normal lumen (Figure 2). For purposes of determining percent vasoconstriction, the vessel diameters measured from the angiogram after intracoronary nitroglycerin (NTG) were defined as the maximally vasodilated state so that: % vasoconstriction (t) = diameter after NTG - diameter at time t ÷ diameter after NTG.

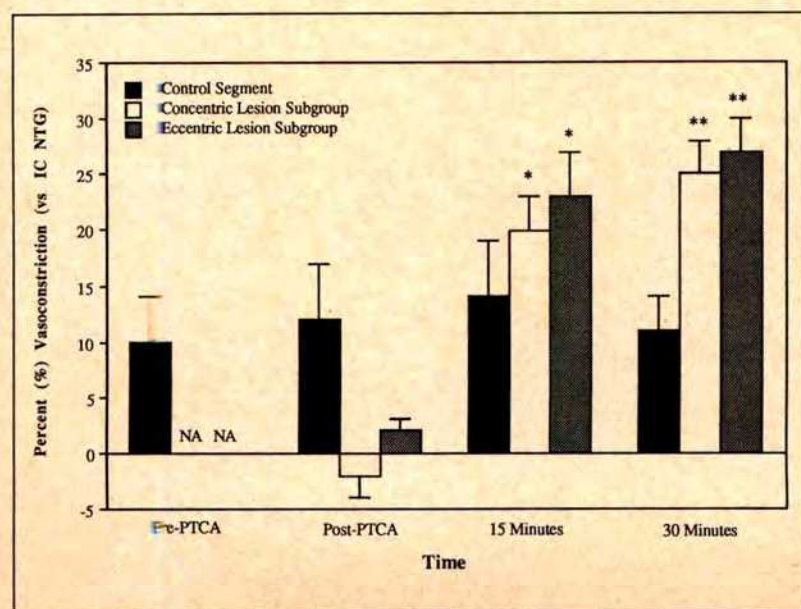


FIGURE 3. Bar graph showing the spontaneous vasoconstrictor responses after percutaneous transluminal coronary angioplasty (PTCA) in the angioplasty segment of the concentric (n = 8) and eccentric (n = 8) lesion subgroups, and in the control segment (n = 12) during the first 30 minutes after PTCA. Vertical bars, percent vasoconstriction (mean ± standard error of the mean) for each segment, defined as the percent change in minimal segmental vessel diameter at each time compared with the diameter 3 minutes after the administration of 300 µg of intracoronary nitroglycerin (IC NTG). There was no significant difference in the degree of vasoconstriction between the concentric and eccentric angioplasty segments at any time point. Vasoconstriction in the angioplasty segment (concentric and eccentric) was significantly greater than that observed in the control segment at 15 and 30 minutes after PTCA (*p < 0.01 and **p < 0.005, respectively). NA = not applicable.

Data are presented as mean \pm standard error unless otherwise stated. Comparisons of percent vasoconstriction in each segment for each condition, lesion eccentricity scores, and patient and procedural variables were analyzed by 1-way analysis of variance, using repeated measures. A p value <0.05 was considered statistically significant.

Nitroglycerin for intracoronary and intravenous administration was prepared by the addition of 25 mg of nitroglycerin (Tridil®) to 250 ml of normal saline solution, yielding a final concentration of 100 μ g/ml. Immediately after the 30-minute arteriogram, 3 ml of this solution were administered as an intracoronary injection via the right or left coronary artery diagnostic catheter.

Of the 16 patients entered into the study, 8 (50%) had coronary lesions that were defined as eccentric based on angiographic criteria (mean a/b eccentricity score, 0.43 ± 0.08). The other 8 patients had lesions that were concentric (mean a/b eccentricity score, 0.81 ± 0.15 , $p < 0.01$ vs eccentric lesion subgroup). The clinical and angiographic characteristics of the 2 groups are described in Table I. There were also no statistically significant differences between the bal-

loon size, number of inflations, measured percent stenosis, or the minimal PTCA lesion diameters before and after intracoronary nitroglycerin between the 2 groups. There were no statistically significant differences between the 2 groups in the type or dosage of medications taken at the time of the study. There were no complications (including myocardial infarction, acute closure, emergent bypass surgery or death) in any patient.

The time course and severity of spontaneous vasoconstriction in the dilated segment is depicted in Figure 3. Individual (raw) data are listed in Table II. The percent vasoconstriction relative to the measurement after intracoronary nitroglycerin is shown for the angioplasty and control segments immediately after PTCA, 15 minutes after PTCA, and 30 minutes after PTCA for the concentric and eccentric lesion subgroups. At 15 and 30 minutes after PTCA there was progressive vasoconstriction of the angioplasty segment in both the concentric and eccentric lesion subgroups, without significant change in basal vasomotor tone (≈ 12 to 15% constricted compared with diameter after intracoronary administration of nitroglycerin) in the control segment. The difference in percent vaso-

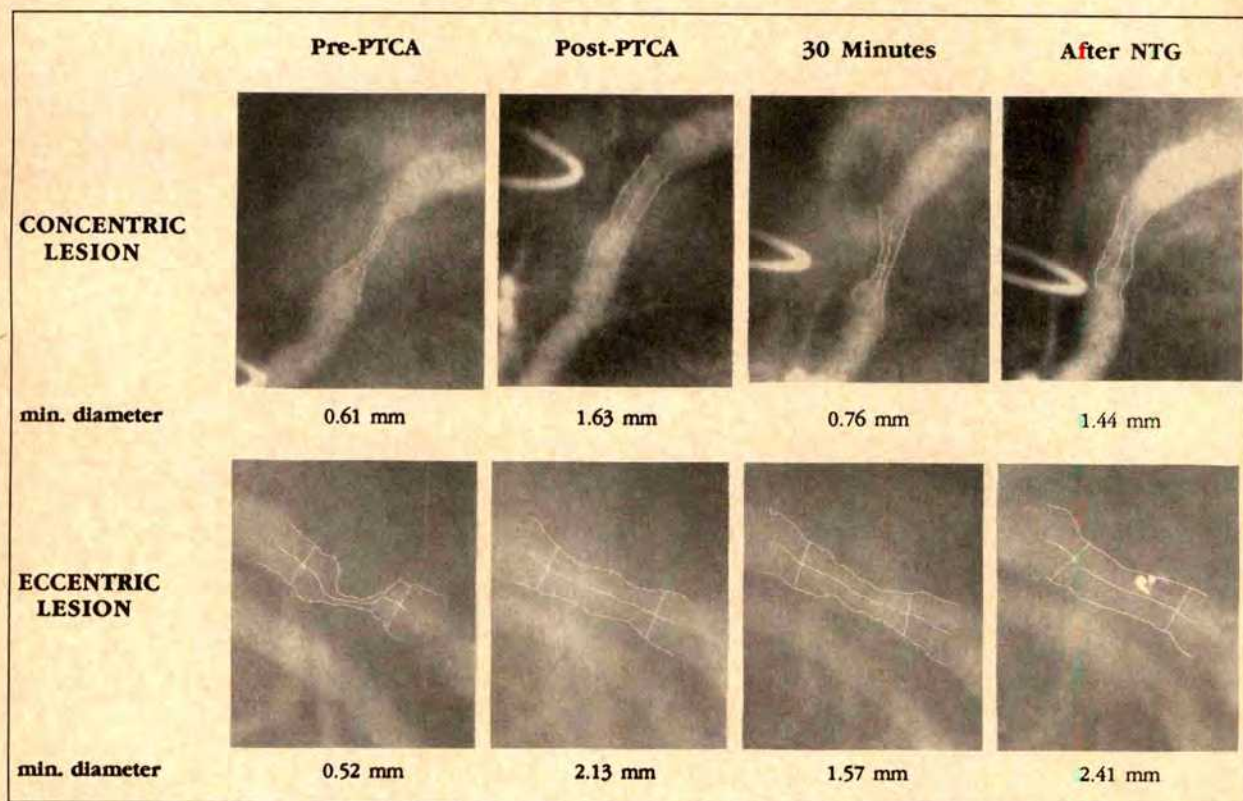


FIGURE 4. Arteriograms showing spontaneous reversible vasoconstriction in the angioplasty segment after percutaneous transluminal coronary angioplasty (Post-PTCA). All images are end-diastolic frames viewed in the same projections and magnification and shown after computerized edge-detection image processing. Examples of both concentric (top row, eccentricity a/b score = 0.92) and eccentric (bottom row, eccentricity a/b score = 0.46) lesions are shown before PTCA (Pre-PTCA), immediately after PTCA (Post-PTCA), 30 minutes after PTCA, and then after intracoronary nitroglycerin (NTG). Minimal (min.) diameters for each segment at each time are shown below angiogram.

constriction of the angioplasty segment between the concentric and eccentric lesion subgroups was not significant (analysis of variance) at any time after PTCA. The degree of vasoconstriction observed in the angioplasty segment of both the concentric and eccentric lesion subgroups were significantly greater than that of the control segment at 15 and 30 minutes after PTCA ($p < 0.01$ and < 0.005 , respectively). Figure 4 shows an example of similar spontaneous vasoconstriction after PTCA in 1 patient with a concentric lesion and in a patient with an eccentric lesion.

This study demonstrates that the severity and incidence of spontaneous vasoconstriction in the dilated segment after PTCA does not differ in eccentric versus concentric lesions. On the basis of these findings we would propose that the "release" of the media from the diseased intima after PTCA may restore more normal vasomotor reactivity in concentrically diseased coronary segments. This hypothesis may explain why the vasoconstriction in the treated concentric lesions is equal to that observed in eccentric lesions, which have an arc of relatively disease-free wall. Were it not for this "releasing" effect of PTCA one might expect the vasoconstrictor and vasodilator responses in these concentrically diseased segments to be limited by circumferential atherosclerosis.¹⁰ The ability of intracoronary nitroglycerin to actively vasodilate the angioplasty segment provides further evidence of improved segmental arterial compliance in concentric lesions after PTCA.

Although lesion eccentricity has been regarded as a "risk factor" for complications after PTCA, this study does not support the notion that these complications are attributable to greater vasospasm in eccentric compared with concentric stenoses. However, given the magnitude of the vasoconstrictor responses observed in some of these

patients, it is likely that spontaneous vasoconstriction after PTCA does contribute to acute closure syndromes after PTCA of both eccentric and concentric lesions.

Despite prior hypotheses to the contrary, coronary lesion eccentricity does not appear to influence the incidence or severity of spontaneous vasoconstriction in the dilated segment after PTCA.

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Edge Detection Versus Videodensitometry for Quantitative Angiographic Assessment of Directional Coronary Atherectomy

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The immediate efficacy of coronary atherectomy should be established by reproducible quantitative coronary analysis.¹ The term "directional atherectomy" suggests that the device can be selectively directed toward the plaque and that its cutting mecha-

nism is potentially less disruptive on vascular architecture than other angioplasty modalities. As a result of this selectively debulking action, the vessel may assume a more circular configuration, and cross-sectional area measurements obtained by edge detection and videodensitometry should become more comparable. This study was undertaken to determine whether videodensitometry and edge detection were equally acceptable methods in assessing the immediate results after atherectomy since the optimal method has not yet been established. Cineangiograms of 20 patients who underwent directional coro-

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nary atherectomy were analyzed with a computer-based coronary angiographic analysis system. The results of the cross-sectional area derived from contour analysis and videodensitometry were compared before and after directional atherectomy.

From September 1989 through September 1990, 55 patients underwent directional coronary atherectomy at the Thoraxcenter. Patients were selected for atherectomy when an eccentric stenosis was present in a proximal coronary artery. This series consists of the initial 20 atherectomy patients (17 men, 3 women). Edge detection and videodensitometry were used to evaluate the immediate results after atherectomy. All patients underwent a successful procedure without preceding or adjunct balloon angioplasty. Patients ranged in age from 42 to 76 years (mean 62). Coronary angiography showed 1-vessel disease in 14 patients, 2-vessel disease in 3 and 3-vessel disease in 3. The site of the obstruction was located in the left anterior descending coronary artery in 10 patients, the circumflex coronary artery in 2, the right coronary artery in 6 and a coronary artery bypass vein graft in 2.

After administration of local anesthesia, an 11Fr sheath was inserted into the femoral artery. All 20 patients received 250 mg of acetylsalicylic acid and 10,000 U of heparin intravenously. Intracoronary injection of isosorbide dinitrate was performed to relieve any possible spasm. After the initial angiograms in multiple views were completed, a special 11Fr guid-

ing catheter was placed into the ostium of the coronary artery. Under fluoroscopy, the guidewire was advanced into the distal part of the artery; then, the atherectomy device was slipped over the guidewire and positioned across the stenosis. After proper positioning, the support balloon was inflated up to 0.5 atm, the cutter was retracted and balloon inflation pressure was increased to 2 to 3 atm. The driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding atherosclerotic lesion in the collecting chamber located at the tip of the catheter. After each pass, the balloon was deflated and either removed or repositioned. On average, 6.7 (3 to 14) passes were performed across a stenosis. Atherectomy was considered successful when the residual stenosis was <50% after tissue retrieval. After atherectomy the arterial and venous sheaths were usually left in place for 6 hours. Patients were monitored for 24 hours, and electrocardiograms and cardiac enzyme levels were obtained twice a day. Nifedipine was administered every 2 hours after the

TABLE I Edge Detection Before and After Directional Atherectomy

	Before Atherectomy	After Atherectomy	p Value
Reference diameter (mm)	3.05 ± 0.55	3.40 ± 0.44	0.05
Obstruction diameter (mm)	1.08 ± 0.43	2.68 ± 0.42	0.000001
Diameter stenosis (%)	66 ± 10	20 ± 9	0.000001

TABLE II Minimal Luminal Cross-Sectional Area Derived from Edge Detection and Videodensitometry Before and After Coronary Atherectomy

Minimal Cross-Sectional Area (mm ²)						
Pt. No.	Before Atherectomy			After Atherectomy		
	ED	VD	Difference	ED	VD	Difference
1	0.70	0.66	0.04	7.60	5.40	2.20
2	1.00	0.56	0.44	6.70	6.90	-0.2
3	0.40	0.26	0.14	6.20	5.00	1.20
4	0.50	0.16	0.34	7.30	7.30	0.00
5	1.10	1.33	-0.23	10.0	9.06	0.94
6	1.60	1.65	-0.05	6.60	2.99	3.61
7	0.60	0.56	0.04	3.20	2.86	0.34
8	0.92	0.67	0.25	4.81	4.22	0.59
9	0.49	0.25	0.24	4.80	4.19	0.61
10	2.70	3.58	-0.88	6.50	5.72	0.78
11	2.00	1.75	0.25	3.90	5.35	-1.45
12	0.70	0.58	0.12	5.70	6.37	-0.67
13	0.90	0.70	0.20	1.80	1.80	0.00
14	1.8	3.4	-1.6	3.30	3.98	-0.68
15	0.5	-0.42	0.92	7.80	7.23	0.57
16	2.60	2.77	-0.17	6.30	5.50	0.80
17	0.60	0.17	0.43	5.20	4.26	0.94
18	1.2	1.6	-0.40	8.50	10.1	-1.60
19	1.79	1.88	-0.09	5.30	5.20	0.10
20	0.33	0.65	-0.32	6.70	4.79	1.91
Mean ± SD -0.01 ± 0.52				Mean ± SD 0.48 ± 1.21		

ED = edge detection; SD = standard deviation; VD = videodensitometry.

procedure and the patients were maintained on aspirin for 1 year.

Quantitative analysis of the stenotic coronary segments was performed with the computer-assisted Cardiovascular Angiographic Analysis System that has been described in detail elsewhere.²⁻⁷ To analyze a coronary arterial segment, a 35-mm cineframe was selected. A region of interest encompassing the arterial segment to be analyzed was electronically digitized (512×512 pixels) with a high-fidelity videocamera. Contours of the arterial segments were detected automatically on the basis of the weighted sum of the first and second derivative functions applied to the digitized brightness profile. From these contours, the vessel's diameter functions were determined by computing the shortest distance between the left and right contour positions. A computer-derived estimation of the original arterial dimension at the site of the ob-

struction was used to define the interpolated reference diameter. This technique is based on a computer-derived estimation of the original diameter values over the analyzed region (assuming there was no disease present) according to the diameter function. Conversion of the diameter measurements of the vessel to absolute values was achieved by using the contrast catheter as a scaling device after correction for pin-cushion distortion. The minimal cross-sectional area of the narrowed segment and the interpolated percent area stenosis were then derived by assuming a circular model and comparing the observed stenosis dimensions with the reference values. The angiographic analysis was done using the average of multiple matched views with orthogonal projections whenever possible.

To determine the changes in cross-sectional area of a coronary segment from the density profile within

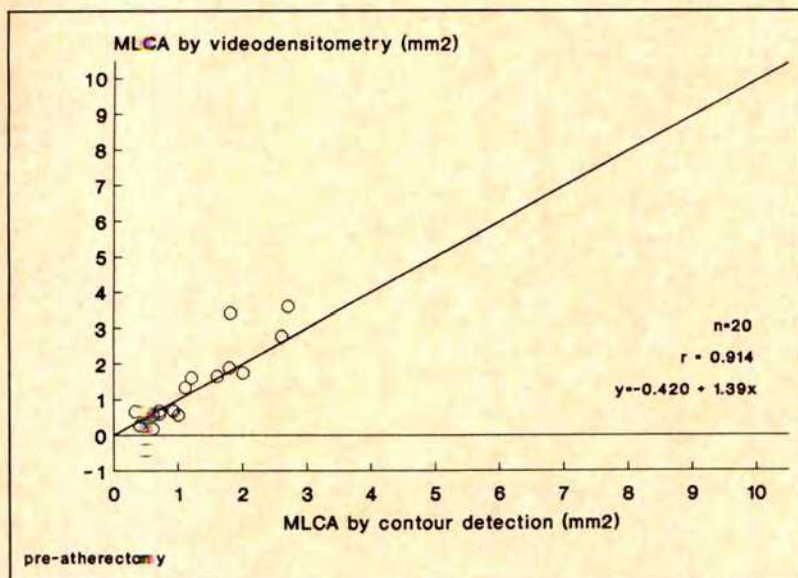


FIGURE 1. Determination of the minimal luminal cross-sectional area (MLCA) by contour detection and videodensitometry before atherectomy. The line represents the line of identity. The correlation coefficient is 0.914 (95% confidence interval: 0.791 to 0.966). The regression equation was $y = -0.420 + 1.39x$.

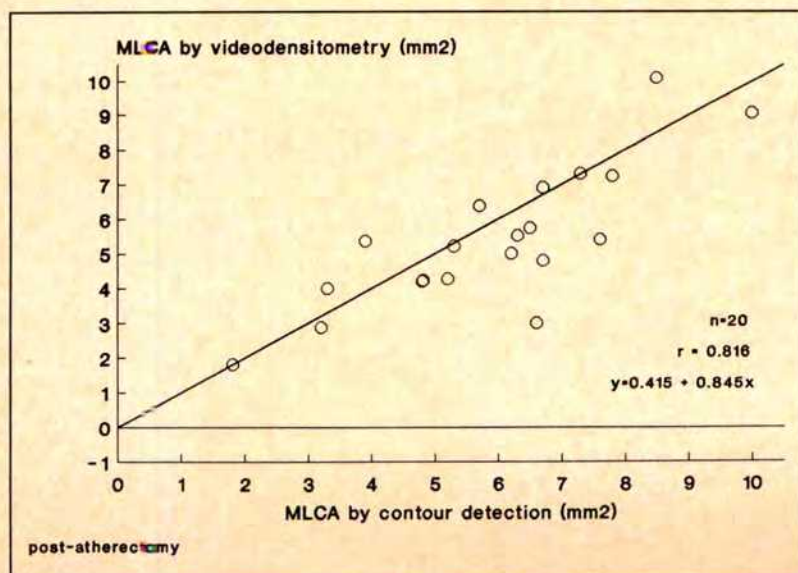


FIGURE 2. Comparison of the minimal luminal cross-sectional area (MLCA) as assessed by contour detection and videodensitometry after atherectomy. The line represents the line of identity. After atherectomy a slight deterioration in the relation is found as is expressed by a lower correlation coefficient (0.816). The regression equation was $y = 0.415 + 0.845x$.

the artery, the calibration of the brightness levels in terms of the amount of x-ray absorption (Lambert Beer's law) is required. The videodensitometric method used with our system corrects for spatially variant responses in the imaging chain and for daily variations in the cinefilm processing. Details of this technique have been described elsewhere.²⁻⁷ Contours of the artery are detected by automated contour detection with the Cardiovascular Angiographic Analysis System, as previously described. Diameter data are derived from the measured diameters along the analyzed segment. On each scan line perpendicular to the centerline of the vessel, a profile of brightness is measured. This profile is transformed into an absorption profile by means of a simple logarithmic transfer function. The background contribution is estimated by computing the linear regression line through the background points directly left and right of the detected contours. Subtraction of this background portion from the absorbed profile within the arterial contours

yields the net cross-sectional absorption profile. Integration of this function gives a measure for the cross-sectional area at the particular scan line. By repeating this procedure for all scan lines, the cross-sectional area function is obtained. A reference densitometric area is obtained using the same principles as described for the diameter functions. Calibration of the densitometric area values is accomplished by comparing the reference area calculated from the diameter measurements (assuming a circular cross-section) with the corresponding densitometric area value. The complete procedure has been evaluated with cinefilms of perspex models of coronary obstructions.⁶

The individual data for diameter and densitometric area measures were used to calculate the mean \pm standard deviation. Analysis of variance was performed to compare the area measurements derived from edge detection (assuming a circular cross-section) and densitometry before and after atherectomy, and when significant differences were found, 2-tailed

FIGURE 3. Individual data of the average minimal cross-sectional area (MLCA) before atherectomy assessed by edge detection and videodensitometry versus the difference in cross-sectional area between the methods. The mean difference before atherectomy was 0.01 mm². SD = standard deviation.

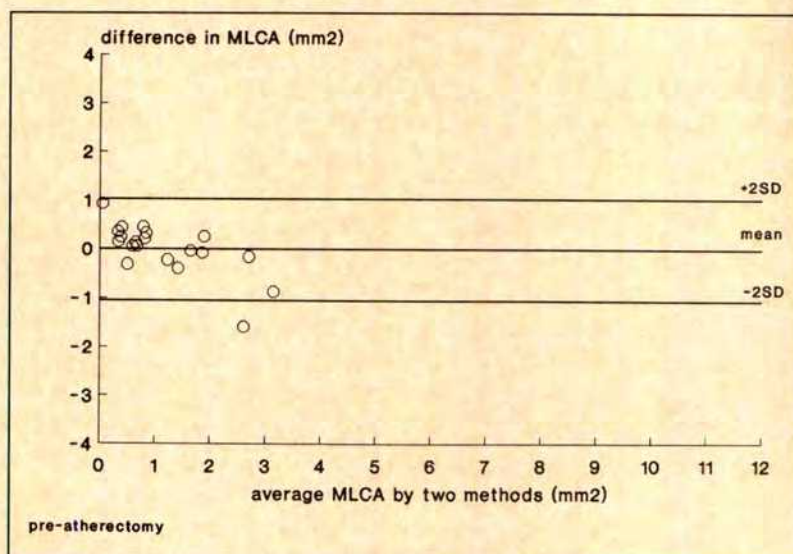
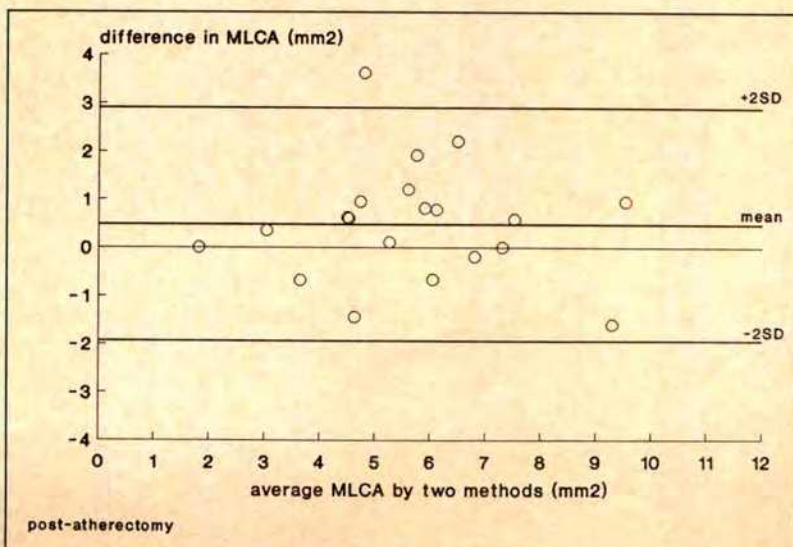


FIGURE 4. Comparison of the average minimal cross-sectional area (MLCA) after atherectomy by edge detection and videodensitometry versus the difference in cross-sectional area between the methods. After atherectomy the difference was slightly higher (0.48 mm²). The variability was larger after than before atherectomy. SD = standard deviation.



paired *t* tests were applied. A statistical probability <0.05 was considered significant. To measure the strength of the relation between the 2 methods of analysis (edge detection and videodensitometry) in the determination of minimal cross-sectional area, the product-moment correlation coefficient (*r*) and its 95% confidence intervals were calculated at 2 distinct times of study. The agreement between the 2 measures was assessed by determining the mean \pm standard deviation of the between-method difference, as suggested by Bland and Altman.⁸ At each interval, this was done by computing the sum of the individual differences between the 2 methods to determine the mean difference \pm standard deviation.

In this study, the angiographic projection with the severest narrowing was analyzed. The individual data obtained by edge detection and videodensitometry are presented in Tables I and II. On average, the reference diameter increased from 3.1 to 3.4 mm ($p = 0.05$); the obstruction diameter increased from 1.1 to 2.7 mm ($p < 0.00001$); thus, the interpolated diameter stenosis was reduced from 66 to 20% ($p < 0.000001$). Quantitative analysis of the atherectomy device showed an increase in its diameter from 2.0 ± 0.2 to 3.4 ± 0.4 mm after inflation of the support balloon. The minimal luminal cross-sectional area determined by densitometry was compared with the minimal luminal cross-sectional area measurements from edge detection which assumes a circular configuration. The comparative data before and after coronary atherectomy are shown in Table II and Figures 1 and 2. The minimal luminal cross-sectional area increased after atherectomy from 1.12 ± 0.72 to 5.91 ± 1.95 mm² ($p < 0.0001$). In patient 15, a coronary artery side branch ran parallel to the stenotic coronary artery and contributed to an increase in the background brightness value. Subtraction of this increased background contribution yielded a negative cross-sectional absorption profile at the site of the coronary artery obstruction. Before atherectomy, the correlation coefficient was 0.914 (95% confidence interval, 0.791 to 0.966), indicating a reasonable linear relationship between the 2 techniques. However, this deteriorated slightly after atherectomy, resulting in a correlation coefficient of 0.816 (95% confidence interval, 0.584 to 0.924). The agreement between the 2 measurements is illustrated in Table II and Figures 3 and 4. The mean difference of the minimal cross-sectional area between the 2 methods before atherectomy was -0.01 mm²; this difference was slightly larger after atherectomy (mean difference 0.48 mm²). The variability as determined by the standard deviation of the between-method difference was higher after (1.21 mm²) than before (0.52 mm²) atherectomy.

The use of quantitative angiographic analysis for assessing both the immediate and long-term results of interventional techniques appears mandatory. Whether edge detection or videodensitometry should be used as the gold standard continues to be debated. Densitometry has been proposed as an alternative method of quantitative assessment of the severity of coronary artery stenosis. It is based on the linear relation that exists between the optical density of a contrast-enhanced lumen and the absolute dimensions of the arterial segment, and is therefore independent of the geometric shape. Discrepancies between edge detection and videodensitometry are most likely to occur when the shape of the vessel wall at the level of the stenosis deviates furthest from a circular configuration, because it is a basic assumption in the calculation of minimal luminal cross-sectional area by edge detection.² Previous studies have shown discrepancies in the analysis between edge detection and videodensitometry after balloon angioplasty.² Since the cutting mechanism of atherectomy is expected to remodel the treated coronary artery into a more concentric and circular configuration, densitometry should correlate closely with the cross-sectional area measurements derived from edge detection.

Because comparing 2 methods in clinical practice should not only be limited to the assessment of the strength of the relation (correlation coefficient, *r*),⁸ we also included the assessment of the degree of agreement or variability, which is determined by the mean \pm standard deviation of the between-method difference. This comparative study illustrates that a linear relation exists between the 2 methods both before and after atherectomy. However, it must be emphasized that the strength of the relation deteriorates slightly after atherectomy. Overall, a good agreement exists between the 2 methods, although edge detection slightly underestimates the minimal luminal cross-sectional area before atherectomy and overestimates the minimal cross-sectional area after atherectomy.

Quantitative coronary angiography shows that a similar discrepancy exists in the postatherectomy analysis between edge detection and videodensitometry when compared with the results in a previous balloon angioplasty study.² This observation suggests that edge detection and videodensitometry are equally acceptable methods for assessing the results of interventional techniques, although small differences exist in the postinterventional analysis. The possible explanation for these differences is the occurrence of trauma to the vessel wall by the interventional devices. This obviously results in the formation of intimal flaps and dissections with subsequent distortion of the vessel configuration. The recoil phenomenon, as assessed after balloon angioplasty, may also play an important role.⁹ Stent implantation apparently counter-

acts these influences by acting as a scaffolding device and by its self-expanding property.^{10,11} This suggests that the cutting mechanism of atherectomy and the barotrauma of balloon angioplasty result in similar eccentric vessel contours.

In conclusion, despite small differences in minimal luminal cross-sectional area after intervention, edge detection and videodensitometry are equally acceptable methods in assessing the immediate results after atherectomy. Atherectomy, as well as balloon angioplasty, induce substantial trauma to the vessel wall, which results in a noncircular vessel configuration. The smoothing process of stenting results in more circular vessel contours compared with balloon angioplasty and atherectomy.

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Effects of Parasympathetic Blockade on Ischemic Threshold in Patients with Exercise-Induced Myocardial Ischemia

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In patients with coronary artery disease (CAD), an abnormal coronary vasoconstriction superimposed to organic stenosis may further limit coronary flow reserve.¹ This functional factor can modulate flow availability to the ischemic region and be responsible for the variability of ischemic threshold frequently observed in patients with effort angina pectoris.² An imbalance between dilatatory and constrictor stimuli has been postulated in these patients, possibly related to the impairment of the endothelium-mediated regulation of smooth muscle tone.³ In normal subjects, coronary infusion of acetylcholine produces coronary vasodilation that appears to be mediated by the endothelium-derived relaxing factors, whereas in patients with CAD, it reduces large coronary artery diameter and decreases coronary flow velocity⁴ (in animal experiments this latter effect seems to be indepen-

dent of both α and β blockade, and is promptly reversed by intravenous injection of atropine).⁵

A similar phenomenon can be observed during exercise. Compared with normal subjects, patients with CAD have a paradoxical vasoconstriction of large epicardial coronary arteries that can be prevented by treatment with isosorbide dinitrate.^{6,7} It can be hypothesized that in normal conditions the parasympathetic system opposes vasoconstriction during exercise, whereas in the absence of endothelium its effect is reversed to coronary vasoconstriction. The aim of this study was to evaluate the effect of atropine, a parasympathetic blocker, compared with that of isosorbide dinitrate, an endothelial independent vasodilating drug, on the ischemic threshold of patients with exercise-induced ischemia.

Seventeen of 23 consecutive patients (14 men and 3 women, mean age \pm standard deviation 54 ± 4 years) with history of effort angina of unchanged severity in the preceding 3 months, typical exercise-induced ST-segment depression and angiographically documented CAD gave informed consent to enter this study.

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TABLE I Clinical Features												
Pt. No.	Age (yr) & Sex	Healed MI	SH	No. CA	Coronary Stenoses (% DR)							LVEF (%)
					LAD	D	LC	M	Right	LM	CC	
1	60M	0	0	1	75	—	—	100	—	—	0	60
2	66M	Inferior	0	3	75	—	75	75	95	—	0	50
3	59M	0	0	1	100	—	—	90	—	—	+	52
4	55F	0	0	2	75	—	—	—	90	—	+	52
5	67M	0	0	2	90	—	—	—	75	—	+	47
6	55F	Inferior	+	2	75	—	—	—	100	—	+	72
7	54M	0	0	2	100	—	100	—	—	—	+	72
8	50M	Inferior	0	3	90	—	75	—	95	—	0	54
9	62M	0	0	2	—	75	—	—	—	75	0	68
10	58M	0	+	3	90	90	50	—	100	—	+	58
11	40M	Anterior	0	3	100	—	50	—	75	—	+	45
12	60F	Inferior	0	3	90	—	90	—	95	—	0	58
13	58M	0	0	2	100	75	—	—	90	—	+	72
14	53M	0	0	1	—	90	—	—	50	—	0	63
15	57M	Inferior	0	1	90	75	—	—	—	—	+	75
16	47M	Inferior	0	1	—	75	—	—	100	—	+	57
17	50M	Inferior	0	3	75	—	50	—	100	—	+	49

CA = diseased coronary arteries; CC = collateral circulation; D = diagonal branch; DR = diameter reduction; LAD = left anterior descending artery; LC = left circumflex artery; LM = left main; LVEF = left ventricular ejection fraction; M = marginal branch; MI = myocardial infarction; Right = right coronary artery; SH = systemic hypertension.

TABLE II Exercise Stress Test Results						
	Basal (B)	ISDN (I)	Atropine (A)	Statistical Analysis		
				B-I	B-A	I-A
Exercise duration (min)	6.6 ± 2.2	8.7 ± 2.3	6.8 ± 2.5	*		*
Time to 0.15 mV ST- (min)	6.2 ± 2.4	8.4 ± 2.3	6.6 ± 2.4	*		*
HR at rest (beats/min)	71 ± 10	85 ± 15	104 ± 11	*	*	*
HR slope (beats/min/min)	6.5 ± 3.7	5.3 ± 1.8	6.2 ± 5.4			
HR at 0.15 mV ST- (beats/min)	112 ± 16	124 ± 33	137 ± 11		*	
Maximal HR (beats/min)	114 ± 15	132 ± 15	139 ± 11	*	*	†
% of max. predicted HR	69 ± 9	81 ± 10	85 ± 7	*	*	†
Systolic BP at rest (mm Hg)	135 ± 16	118 ± 11	125 ± 14	*	†	
Systolic BP slope (mm Hg/min)	6.6 ± 2.3	8.4 ± 3.1	7.9 ± 3.9			
Systolic BP at 0.15 mV ST-	176 ± 20	185 ± 25	173 ± 22			*
Max. systolic BP (mm Hg)	181 ± 18	190 ± 25	174 ± 23	†		
RPP at rest (mm Hg · beats/min)	9,695 ± 2,236	9,983 ± 2,138	13,000 ± 2,239		*	*
RPP slope (mm Hg · beats/min/min)	1,632 ± 690	1,732 ± 660	1,885 ± 1,218			
RPP at 0.15 mV ST-	19,829 ± 4,681	24,185 ± 5,207	23,732 ± 4,088	*	*	
Max. RPP (mm Hg · beats/min)	20,682 ± 4,420	25,228 ± 5,153	24,319 ± 4,396	*	*	
Max. ST shift (mV)	0.19 ± 0.05	0.19 ± 0.09	0.20 ± 0.08			

Basal = baseline test; BP = blood pressure; HR = heart rate; ISDN = isosorbide dinitrate; Max. = maximal; RPP = rate-pressure product; ST- = ST-segment depression.

The presence of associated pathologic conditions that could interfere with the interpretation of ST shift during exercise were carefully excluded. Table I lists the clinical and angiographic characteristics of the study patients.

After a period of pharmacologic washout of ≥72 hours, all patients performed 3 exercise stress tests on 3 consecutive days. The tests were performed after intravenous administration of 1 mg of atropine, 1 mg of isosorbide dinitrate and 2 ml of normal saline solution. The sequence of drug administration was randomized. Tests were always performed in the morning and ≥3 hours after administration of sublingual nitrates when required. Patients performed exercise on an electromagnetic bicycle with load increments of 25

W every 2 minutes. At baseline, during exercise and during the recovery phase (≥5 minutes, allowing for normalization of the electrocardiogram), 12-lead electrocardiogram and blood pressure (cuff sphygmomanometer) were recorded every minute; 3 electrocardiographic leads were continuously monitored throughout the test. Criteria for test interruption included clear-cut ischemic ST-segment depression (>0.2 mV) with or without anginal pain, significant decrease in systolic blood pressure during exercise, severe dyspnea, troublesome ventricular arrhythmias, maximal age-related heart rate and muscular exhaustion. Tests began 5 minutes after intravenous drug administration. Analysis of ST-segment trends was retrospectively, independently and blindly per-

formed by 2 of the investigators. They had to identify both the time of onset of ischemia, defined as the time corresponding to ST depression of 0.15 mV, 0.08 second after J point and the maximal ST-segment shift. Agreement was found in 94% of tests.

The following ergometric parameters were considered for analysis: time to onset of ischemia; heart rate; systolic blood pressure; and rate-pressure product at rest, at the onset of ischemia and at peak exercise. As previously described, the rate of increment during exercise of heart rate, systolic blood pressure and rate-pressure product were obtained from the linear regression between time of exercise and the corresponding values of each parameter.² Comparisons were performed using analysis of variance for repeated measurements; *p* values <0.05 were considered significant. Data were expressed as mean \pm standard deviation.

All patients performed the 3 exercise stress tests without any complications. The mean values \pm standard deviations of ergometric variables and the results of statistical analysis are listed in Table II. At rest, the intravenous administration of 1 mg of atropine, compared with that of saline solution, resulted in a significant increase in heart rate from 71 ± 10 to 104 ± 11 beats/min (*p* <0.01) and a slight but significant reduction in systolic blood pressure from 135 ± 16 to 125 ± 14 mm Hg (*p* <0.05). As a consequence, rate-pressure product at rest increased from $9,695 \pm 2,236$ to $13,000 \pm 2,239$ mm Hg \cdot beats/min (*p* <0.01). The administration of 1 mg of isosorbide dinitrate induced an increase in heart rate at rest from 71 ± 10 to 85 ± 15 beats/min (*p* <0.01) and a concomitant decrease in systolic blood pressure from 135 ± 16 to 118 ± 11 mm Hg (*p* <0.01); rate-pressure product was unchanged from its baseline value. Both atropine and isosorbide dinitrate did not influence the rate of

increment of heart rate, systolic blood pressure and rate-pressure product during exercise compared with placebo. Onset of ischemia was reached at a significantly higher rate-pressure product with both atropine and isosorbide dinitrate than during the baseline test (Figure 1, Table II). Atropine produced this effect with a significant increase in heart rate at ischemia (112 ± 16 vs 137 ± 11 beats/min, *p* <0.01), whereas isosorbide dinitrate produced the same effect, but with a slight, although not significant, increase in both heart rate and systolic blood pressure. Exercise time to ischemia was increased by isosorbide dinitrate only compared with that during baseline test (6.2 ± 2.4 to 8.4 ± 2.3 minutes, *p* <0.01). Atropine, despite the significant improvement in rate-pressure product at ischemia, did not increase exercise time to ischemia because of the simultaneous increase in resting rate-pressure product (Figure 2).

Results from this study show that atropine and isosorbide dinitrate both induced a significant and similar increment in rate-pressure product at ischemia compared with placebo. Based on the assumption of a linear relation between rate-pressure product and myocardial oxygen consumption, an increase in myocardial blood flow due to coronary vasodilation could be postulated, even if variations of cardiac volume and contractility, 2 additional determinants of oxygen consumption, are ignored. Several studies have documented that coronary vasocon-

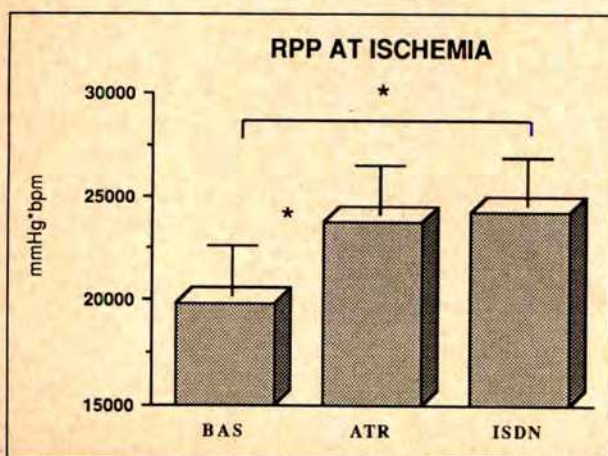


FIGURE 1. Compared with baseline test (BAS), both atropine (ATR) and isosorbide dinitrate (ISDN) significantly increased, and to the same extent, rate-pressure product (RPP) at ischemia (ischemic threshold).

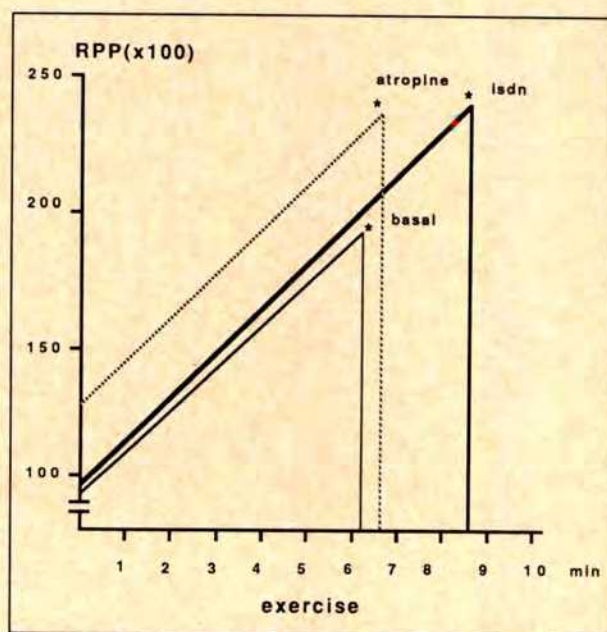


FIGURE 2. Schematic representation of the effects of intravenous administration of atropine (1 mg) and isosorbide dinitrate (ISDN) (1 mg), compared with baseline test (basal), on rate-pressure product (RPP) at rest and at ischemia (asterisk), and time to ischemia. Atropine did not increase time to ischemia because the improvement in ischemic threshold was obviated by the negative effect on myocardial oxygen consumption (higher rate-pressure product at rest and at each level of exercise).

striction can contribute to reducing coronary flow availability during exercise in patients with CAD.^{2,6} Using quantitative angiography, Brown⁶ and Gage⁷ and their co-workers were able to show a worsening of the stenosis during exercise and its prevention by nitroglycerin administration. This phenomenon may account for the short-term variability of the ischemic threshold frequently observed in patients with effort angina and for the increase in ischemic threshold after administration of nitrates and calcium antagonists.² This inappropriate coronary vasoconstriction has been attributed to the increment of α -sympathetic tone during exercise.⁶ The role of α stimulation in the attenuation of flow response to exercise has been documented in experimental studies, whereas the therapeutic effect of α blockade on effort and resting angina is negligible.

The recent observation of Furchgott and Zawadzki⁸ on the key role of the endothelium in the regulation of coronary vascular tone has focused attention on the tone disturbances in deendothelialized coronary atherosclerotic vessel segments. Evidence exists indicating that the endothelium is the source of the endothelium-derived relaxing factor that counterbalances direct constrictor stimuli of the vessel's muscular wall. Several agents, such as acetylcholine, blood cell products, neuropeptides, hormones and physicochemical stimuli, have at the same time been shown to exert an endothelium-mediated vasodilating effect and a direct constrictor effect on vascular smooth muscle.³ The recent experimental demonstration that adventitial application of acetylcholine on both femoral arteries and coronaries can produce an endothelium-mediated dilation⁹ gives the key for a possible pathophysiologic interpretation of the impairment of both local acetylcholine and flow-mediated mechanisms leading to coronary dilation in CAD.¹⁰ On this basis, an increased coronary tone during exercise might be related to the persistence of a direct parasympathetic coronary constriction that is not balanced by an adequate production of endothelium-derived relaxing factor.

In conclusion, from the results of this study a role of parasympathetic vasoconstriction of atherosclerotic coro-

nary segments in patients with exercise-induced ischemia can be postulated. However, atropine can not be proposed as a drug for treatment of effort ischemia because of its concomitant effect on myocardial oxygen consumption. Further studies are needed to ascertain, in a more direct way, the effect of parasympathetic blockers on normal and diseased coronary segments during exercise. If parasympathetic vasoconstriction of diseased coronary vessels during exercise can be confirmed, the search for antimuscarinic agents with selective effect on coronary vessels, but not on sinus node automaticity, could be worthwhile from the perspective of defining an alternative physiologic approach to the treatment of effort ischemia.

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Long-Term Follow-Up After Intracoronary Ethanol Ablation of Atrioventricular Conduction

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Recently we reported on the chemical ablation of atrioventricular (AV) conduction by selective injection of pure ethanol into the AV nodal coronary artery.¹ In this communication we would like to report on the long-term follow-up of this intervention in 11 patients.

All 11 patients had paroxysmal ($n = 9$) or permanent ($n = 2$) atrial flutter or fibrillation. Electrical ablation of AV conduction had unsuccessfully been attempted in 8 patients. The method of identification and selective catheterization of the AV nodal coronary artery has been previously described.¹ In following the observation that the injection of iced saline solution through the catheter resulted in high-degree or complete AV block, we gave 11 patients an injection of 0.3 to 3 ml of 96% ethanol. Because of our experience with backflow of alcohol along the catheter leading to inferior myocardial infarction (patient 4),¹ we carefully checked backflow after fluid injection through the catheter in the last 7 patients by administering iodinated contrast before alcohol was given. In all patients cardiac enzymes were obtained every 6 hours for ≥ 2 days after ethanol injection. Pacing by way of a transvenous temporary right ventricular apical pacing catheter was performed for 2 days. During that time

ventricular pacing was interrupted a few times each day to check AV conduction. If complete or high-degree (ventricular rate less than twice the sinus rate) AV block was still present after 2 days, a permanent transvenous pacemaker was implanted.

The type of pacemaker (DDDR or VVIR) was selected after the atrial contribution to ventricular performance was evaluated by echo-doppler measurements.

In all patients complete or high-degree AV block was accomplished acutely by selective ethanol injection into the AV nodal coronary artery. One patient in a previous report¹ regained normal AV conduction within 24 hours and a second injection of alcohol was given, which not only resulted in complete AV block probably because of backflow of ethanol along the catheter, but also in an inferior myocardial infarction. Two of the remaining 10 patients had recurrence of AV conduction after 7 and 28 days, respectively. A coronary angiogram recorded after recurrence of nodal AV conduction showed an occlusion of the AV nodal coronary artery in 1 patient and a vessel still open in the other. During a follow-up period of 5 to 20 months (mean 10.3), the other 8 patients all had persistence of the same degree of complete or high-degree AV block. Ventricular rates varied from 40 to 65 beats/min. In the 1 patient who received alcohol twice in the AV nodal coronary artery, complete AV block was still present 17 months after the second injection.

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TABLE 1 Clinical Characteristics of the 11 Patients Studied

Pt.	Age (yr) & Sex	Ethanol (ml)	SGOT Max.	Rhythm After Ablation		F/U (mo)
				Initial	Long-Term	
1	70F	2	85	CHB		20
2	64F	2	96	CHB		20
3	64M	2.5	65	HDB	AF, VR* < 100 beats/min	
4†	69F	1	28	CHB	1:1 AV cond. after 12 hours	
		2	363	CHB		17
5	60M	3	37	CHB	AF, VR* < 100 beats/min	
6	69M	0.5	29	CHB		14
7	54M	0.5	220	CHB		12
8	56M	1.2	25	HDB		10
9	54M	0.5	25	HDB		7
10	58M	0.3	42	CHB		6
11	58M	1.2	37	CHB		5

*Patient had return of atrioventricular conduction after 7 (patient 3) and 28 days (patient 5).

†Patient received ethanol twice.

AF = atrial fibrillation; AV = atrioventricular; CHB = complete heart block; cond. = conduction; F/U = follow-up; HDB = high-degree block; Max. = maximal; SGOT = serum glutamic oxalacetic transaminase; VR = ventricular rate.

All 11 patients had a narrow QRS complex immediately after chemical ablation and during their last follow-up visit.

No correlation was found between persistence of complete or high-degree AV block and the amount of alcohol injected or the maximal postablation cardiac enzyme value (Table I). On echocardiographic examination, apart from patient 4 who developed inferior myocardial infarction, only patient 7 had (in the absence of QRS-T changes) a small area of hypokinesia in the inferoposterior region of the left ventricle.

In 9 of the 11 patients, a similar degree of AV block was present immediately and a mean of 10.3 months after injection of 96% ethanol into the AV nodal coronary artery. In one of these 9 patients, a second injection of alcohol was required to obtain permanent AV block. This suggests that in 72% of patients in whom the AV nodal coronary artery can be catheterized, permanent complete or high-degree AV block can be accomplished by a single injection of alcohol. Recurrence of 1:1 AV conduction was observed in 3 patients: in 1 (who subsequently received a second injection of ethanol) within 24 hours and in the other 2 after an interval of 7 and 28 days, respectively. This suggests that if AV conduction recurs, it does so within 1 month after the procedure. The amount of alcohol injected into the AV nodal artery did not appear to be related to the result or to the maximal postablation serum glutamic oxalacetic transaminase value. Apart from patient 4 who developed inferior

myocardial infarction, only 1 patient had a maximal serum glutamic oxalacetic transaminase value >100 U. This patient had no QRS-T changes, but a small hypokinetic area in the posteroinferior region was seen on echocardiographic examination.

We believe that transcatheter ablation of AV conduction should still be considered an experimental procedure. The optimal dose, concentration and speed of injection of alcohol is not known. Refinements in catheter design may lead to greater safety of the procedure. Also, its value compared with electrical ablation of AV conduction is not clear. Whereas high-energy electrical ablation of the AV junction is not without morbidity and mortality,² the use of radiofrequency energy is promising because it allows a safer, gradual, better-controlled modification or interruption of AV nodal conduction.^{3,4} A place for chemical ablation in creating permanent AV block therefore needs to be established.

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Actuarial Risk of Sudden Death While Awaiting Cardiac Transplantation in Patients with Atherosclerotic Heart Disease

DEFIBRILAT Study Group

The problem of sudden death in patients with advanced heart failure¹⁻³ is brought into especially sharp relief when it occurs among patients awaiting cardiac transplantation. Preliminary observations suggest that the implantable cardioverter-defibrillator can be used empirically as a "bridge" to transplant in patients who survive cardiac arrest from sustained ventricular tachyarrhythmias while awaiting a donor heart.⁴ It is therefore reasonable to consider undertaking a clinical trial that would scientifically assess the effectiveness of prophylactic implantable cardioverter-defibrillator therapy in patients awaiting cardiac transplantation.

The design of such a bridge-to-transplant trial necessitates a realistic estimation of the actuarial risk of sudden death in an appropriate group of patients awaiting cardiac transplantation. To obtain the requisite actuarial data, we chose to focus on patients with atherosclerotic heart disease rather than those with nonischemic dilated cardiomyopathy because (1) recent observations⁵ suggest that terminal ventricular tachyarrhythmias may play a more significant role in precipitating cardiac death in heart failure patients with atherosclerotic heart disease, and (2) electrophysiologic testing holds greater promise in the setting of atherosclerotic heart disease for selecting patients at risk for sudden tachyarrhythmic death.^{6,7}

All patients placed on cardiac transplantation waiting lists at 11 centers, from January 1, 1988, through December 31, 1989, were considered for inclusion in the study. An additional entry criterion was New York Heart Association (NYHA) functional class III or IV at the time the patient was placed on the waiting list. Patients were excluded if they had a history of cardiac arrest or documented sustained ventricular tachyarrhythmias, or if they had undergone implantation of a total artificial heart.

Patient outcome was classified into 1 of 3 categories: transplanted, dead before transplantation, or alive at last follow-up but not yet transplanted. The cause of death was further subclassified into the following categories: sudden — unexpected death within

an hour of change in symptoms, or unwitnessed in a previously compensated patient; cardiac nonsudden — any death of cardiac origin but not qualifying as sudden; and noncardiac — death considered not to be of cardiac origin.

Three hundred nine patients formed the study population. Median age was 54 years (range 23 to 66) and 88% were men. The median duration of follow-up was 84 days (range 1 to 860). The number of events occurring over this time period are summarized in Table I. The crude sudden death rate while awaiting transplantation (number of sudden deaths divided by number of patients placed on list) was 11% for the entire study population, but according to functional class was 14 and 6%, respectively, for NYHA class III and IV patients. Sudden death constituted a greater proportion of the total mortality in class III (61%) versus class IV (21%) patients, but a greater proportion of class IV patients were transplanted during follow-up. There were no significant differences in age or sex between class III and IV patients.

Estimated actuarial event rates at 6 and 12 months, using a Kaplan-Meier analysis, are summa-

TABLE I Outcome in Patients with Atherosclerotic Heart Disease Placed on Cardiac Transplantation Waiting Lists at 11 Medical Centers

Outcome	Class III (n = 181)	Class IV (n = 128)	Total (n = 309)
Underwent transplantation (%)	96 (53)	80 (63)	176 (57)
Died while on list (all causes) (%)	41 (23)	39 (30)	80 (26)
Sudden death (%)	25 (61)	8 (21)	33 (41)
Cardiac nonsudden (%)	14 (34)	25 (64)	39 (49)
Noncardiac/unknown (%)	2 (5)	6 (15)	8 (10)
Still awaiting transplantation (%)	39 (22)	6 (5)	45 (15)
Removed from list (%)	5 (3)	1 (1)	6 (2)
Lost to follow-up (%)	0 (0)	2 (2)	2 (1)

TABLE II Actuarial Event Rates (% ± SE) Among 309 Patients with Atherosclerotic Heart Disease Awaiting Cardiac Transplantation

Event	At 6 Months		At 12 Months	
	Class III	Class IV	Class III	Class IV
Death				
Sudden	14 ± 3	18 ± 7	21 ± 4	18 ± 7
Nonsudden cardiac*	7 ± 2	28 ± 5	9 ± 3	37 ± 8
All-cause*	21 ± 4	46 ± 7	29 ± 4	53 ± 7
Transplantation*	41 ± 4	72 ± 5	59 ± 4	80 ± 5

*p < 0.0002 class III vs. IV, log-rank test.
SE = standard error.

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*See Appendix for list of participants.

rized in Table II. While the sudden death rate was similar for Class III and IV patients, the nonsudden cardiac death rate at 12 months in class IV patients was approximately 4 times that of class III enrollees. The cumulative transplant rate among class IV patients was also significantly greater, with a median time to transplant of 8.3 months (range 0 to 23) versus 2.9 months (range 0 to 23) in class III patients ($p < 0.0001$ log-rank test).

This multicenter retrospective analysis indicates that patients with advanced heart failure due to atherosclerotic heart disease face approximately a 20% cumulative 1-year risk of sudden death while awaiting cardiac transplantation. Although congestive heart failure treatment and antiarrhythmic therapy (if present) were not controlled, and hemodynamic and biochemical parameters were not available for analysis, the study population represents a broad cross-section of patients placed on cardiac transplantation waiting lists at centers around the country over a very recent time period. Interestingly, the actuarial risk of sudden death at 1 year, estimated from our study, is virtually identical to that of the recently reported University of California, Los Angeles, experience involving 62 patients evaluated for cardiac transplantation.⁸

Our results have important implications for the design of a bridge-to-transplant study in patients with atherosclerotic heart disease. The high nonsudden cardiac death rate as well as the higher cumulative transplantation rate for NYHA class IV patients suggest that it would be very difficult to demonstrate any benefit of prophylactic implantation of an implantable cardioverter-defibrillator in that subpopulation. The fact that operative mortality related to defibrillator implantation is likely to be greater in these persons⁹ argues further against participation of class IV patients in a bridge-to-transplant trial. By contrast, we found that sudden death accounted for a greater proportion of cardiac and all-cause mortality among NYHA class III patients, consistent with previous observations.³ Thus, a bridge-to-transplant trial using an implantable defibrillator will be most efficient if undertaken exclusively in NYHA class III patients. Our data on actuarial risk of sudden death may be used to estimate what proportion of these patients potentially might benefit from defibrillator therapy (i.e., those who will succumb to sustained ventricular tachyarrhythmias). Such estimates, in turn, can serve as

the basis for realistic power calculations in the design of future bridge-to-transplant trials.

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APPENDIX

DEFIBRILAT (DEFibrillator as BRidge to LAtter Transplantation) Study Group: Michael H. Lehmann, M.D., Principal Investigator. *Participating centers and investigators:* Brigham and Women's Hospital, Boston: Peter L. Friedman, MD, PhD. Loyola University Medical Center, Maywood: David J. Wilber, MD. Medical College of Virginia, McGuire VA Medical Center, Richmond: Kenneth A. Ellenbogen, MD. Minneapolis Cardiology Associates, Minneapolis: Adrian K. Almquist, MD. Presbyterian University Hospital, Pittsburgh: Robert Hardesty, MD; Barry F. Uretsky, MD; Patrick J. Tchou, MD. Stanford University Medical Center, Stanford: L. Bing Liem, DO; Michael B. Fowler, MD. University of Alabama at Birmingham, Birmingham: Andrew E. Epstein, MD. University of Florida, Gainesville: Anne B. Curtis, MD; Edward D. Staples, MD. University of Michigan Medical Center, Ann Arbor: Hugh Calkins, MD. Washington University School of Medicine, St. Louis: Bruce D. Lindsay, MD. Wayne State University/Harper Hospital, Detroit: Michael H. Lehmann, MD; Barbara S. Fromm, MA; Russell T. Steinman, MD; Marc D. Meissner, MD; Claudio D. Schuger, MD.

Aging and Left Ventricular Function in Elderly Healthy People

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Cardiovascular disease is the leading cause of morbidity and mortality in old age. The use of noninvasive methods has increased the possibility of distinguishing between cardiac disease and changes in left ventricular (LV) structure and function related to normal physiologic aging. Knowledge of age-related changes in the heart is mainly acquired from cross-sectional studies¹⁻⁷ and few subjects >75 years of age have been studied. The high prevalence of cardiovascular disease in the elderly makes it difficult to find healthy study subjects aged >75 years. Results from several cross-sectional studies show that aging is associated with increased LV mass and disturbed LV diastolic filling. Data from the Framingham study indicate that increased LV mass may not be an inevitable consequence of aging in a healthy population.⁷ The aim of this longitudinal investigation of healthy men and women, aged >75 years and derived from representative population samples, was to study the influence of aging on LV structure and function over a 4-year period.

The population study "70-year-old people in Gothenburg" is a longitudinal study, initiated in 1971, with a representative sample comprising 30% of the 70-year-old population in the city ($n = 1148$, participation rate 85%). From 1976 to 1977, another sample of 70-year-old patients ($n = 1281$, participation rate 81%) was examined. The surviving persons from these samples have been followed longitudinally up to ages 85 and 79, respectively.⁸ Two subsamples of healthy men and women at ages 75 and 81 years, respectively, were selected according to the following exclusion criteria: history of myocardial infarction; history of stroke; angina pectoris, according to Rose⁹; congestive heart failure; diabetes mellitus; treatment with cardiovascular drugs; chronic obstructive lung disease; malignant disease during the last 5 years; dementia; pathologic electrocardiogram, according to the Minnesota code¹⁰—major Q waves (Minnesota codes 1.1, 1.2), left bundle branch block (7.1), ST-T depression ≥ 0.5 mm (4.1, 4.2), negative or biphasic T waves (5.1, 5.2) or atrial fibrillation (8.3); diastolic blood pressure >95 mm Hg; and increased relative heart volume on chest x-ray or other serious disease.

The 2 study groups of healthy subjects, examined at ages 75 (11 men and 20 women) and 81 (19 men and 17 women), were followed over 4 years and reexamined at ages 79 and 85, respectively. At age 79, 1 man and 4 women were excluded owing to disease (3 cardiovascular disease, 1 dementia, 1 serious coxarthrosis), and 2 men and 7 women refused to participate. Among the subjects included at age 81, 4 men and 1 woman (14%) had died before age 85. Four men and 5 women were excluded at age 85 owing to disease (7 cardiovascular disease, 1 dementia, 1 rectal tumor), and 1 man and 4 women did not wish to participate. This report is restricted to 8 men and 9 women, investigated at ages 75 and 79, and 10 men and 7 women, investigated at ages 81 and 85. All these subjects were without definable disease both at inclusion and at longitudinal follow-up 4 years later.

A noninvasive heart examination including recording of blood pressure and heart rate, electrocardiography, echocardiography, apexcardiography, phonocardiography and carotid pulse tracing was performed at inclusion and after 4 years. Resting blood pressure was measured in the supine position using the Hawksley random zero equipment. Diastolic blood pressure was defined as Korotkoff phase 5. Blood pressure was calculated from duplicate measurements and determined to the nearest 2 mm Hg.

All noninvasive investigations were performed by 2 investigators according to a standardized schedule. Two-dimensional echocardiographic recordings of routine views were made as a guidance for the M-mode echocardiographic recordings. No regional wall motion abnormality was seen on the 2-dimensional echocardiograms during either period. Echocardiography was performed using an IREX system II recorder, with the patient in the left lateral position and with the bed head raised approximately 30°. LV internal diameter and septal and posterior wall thicknesses were measured at the peak of the R wave in the electrocardiogram and at the point of the shortest distance between septal and posterior wall during systole. The leading edge to leading edge method was used. Calculation of LV mass and LV ejection phase indexes was based on the assumption that the left ventricle may be geometrically represented as a prolate ellipsoid.¹¹ LV mass was corrected for body surface area and height. LV peak and end-systolic meridional wall stresses were estimated as previously described.¹¹ The apexcardiogram was recorded from

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TABLE I Left ventricular Morphology and Function (mean \pm standard deviation) in Healthy Men and Women Followed Longitudinally During Four Years

	Baseline (n = 34)	Follow-Up (n = 34)	75 Years (n = 17)	79 Years (n = 17)	81 Years (n = 17)	85 Years (n = 17)
Body mass index (kg/m ²)	25.1 \pm 4.1	24.7 \pm 3.9	24.7 \pm 3.7	24.0 \pm 3.4	25.6 \pm 4.5	25.3 \pm 4.4
Systolic blood pressure (mm Hg)	154 \pm 16	169 \pm 23	148 \pm 15	165 \pm 22	159 \pm 17	173 \pm 24
Diastolic blood pressure (mm Hg)	77 \pm 7	84 \pm 10	77 \pm 7	85 \pm 11	78 \pm 8	84 \pm 9
Heart rate (beats/min)	68 \pm 11	63 \pm 8	72 \pm 12	64 \pm 8	64 \pm 8	63 \pm 8
LV diameter _d (mm)	52.9 \pm 4.4	50.7 \pm 5.7	52.7 \pm 4.2	50.1 \pm 5.4	53.3 \pm 5.0	51.7 \pm 6.3
LV diameter _s (mm)	33.5 \pm 5.2	31.1 \pm 4.6	33.3 \pm 5.6	30.7 \pm 5.0	33.8 \pm 5.0	31.9 \pm 3.8
VS + LV posterior wall _d (mm)	20.7 \pm 2.8	22.7 \pm 3.4	21.2 \pm 3.0	22.0 \pm 2.8	19.9 \pm 2.4	23.8 \pm 4.1
VS + LV posterior wall _s (mm)	31.9 \pm 3.8	33.1 \pm 3.8	32.8 \pm 3.9	32.7 \pm 3.8	30.6 \pm 3.3	33.8 \pm 4.0
LV mass (g)	217 \pm 53	224 \pm 55	221 \pm 55	214 \pm 49	210 \pm 52	242 \pm 62
LV mass/BSA (g/m ²)	122 \pm 29	127 \pm 31	123 \pm 33	120 \pm 25	121 \pm 23	140 \pm 38
LV mass/height (g/m)	130 \pm 29	134 \pm 33	130 \pm 31	126 \pm 27	128 \pm 28	148 \pm 39
Left atrium (mm)	41.2 \pm 5.3	44.0 \pm 5.5	41.2 \pm 6.2	42.7 \pm 7.1	41.2 \pm 4.4	45.4 \pm 2.3
A ₂ O (%)	119 \pm 15	123 \pm 15	121 \pm 15	122 \pm 14	117 \pm 15	125 \pm 17
Fractional shortening (%)	36.9 \pm 5.7	38.7 \pm 4.1	37.1 \pm 5.8	38.9 \pm 5.0	36.6 \pm 5.6	38.4 \pm 1.9
Mean V _{CF} (cm/s)	1.17 \pm 0.21	1.22 \pm 0.16	1.19 \pm 0.22	1.23 \pm 0.17	1.13 \pm 0.20	1.20 \pm 0.15
End-systolic σ S (10 ³ dynes/cm ²)	38 \pm 11	36 \pm 10	36 \pm 11	36 \pm 11	40 \pm 11	36 \pm 9
Peak-systolic σ VS (10 ³ dynes/cm ²)	221 \pm 49	218 \pm 72	209 \pm 48	212 \pm 62	242 \pm 47	228 \pm 91

A₂O% = left ventricular relaxation time; BSA = body surface area; d = diastole; LV = left ventricular; s = systole; V_{CF} = velocity of circumferential fiber shortening; VS = ventricular septal; WS = wall stress.

the point of maximal cardiac impulse, simultaneously with the phonocardiogram and electrocardiogram in relaxed expiratory apnea, with the patient in a left lateral position. The distance between the aortic component of the second heart sound (A₂) to the O point of the apexcardiogram (A₂O interval) was also measured.¹² Since the A₂O interval varies with heart rate, this interval was also expressed as a percentage of the

expected value at the observed heart rate (A₂O% defined as "LV relaxation time index") using the regression equation: A₂O expected = 179 - 0.815 \times observed heart rate. This regression equation was derived from the relation between heart rate and A₂O, determined in a reference group of 49-year old men, in which the mean value for A₂O% was defined as 100%.¹²

The main analysis concerns all 34 subjects, comparing baseline data with the 4-year follow-up data. For descriptive purposes, subgroup analyses have been performed for the 2 age groups and for both sexes. Paired permutation t test was used to test the hypothesis of no difference between baseline and follow-up measurements. A value of $p < 0.05$ was considered statistically significant (2-sided).

Significant increases in systolic and diastolic blood pressures were found during the 4-year follow-up, together with a slight decrease in heart rate (Table I, Figure 1). The subgroup analyses showed significant increases in systolic and diastolic blood pressures in both men and women and also in the 2 age groups. LV wall thickness increased significantly during the 4-year period. LV diameter in systole and diastole decreased significantly. No significant change in LV mass was found. The subgroup analyses showed a significant increase in wall thickness in men and also in all subjects aged 81 to 85 years. A significant increase in left atrial diameter was found during follow-up. This increase was significant also in the separate analysis of subjects aged 81 to 85 years. There was a tendency, although not significant, for prolongation of LV relaxation time. The systolic LV function remained unchanged during the 4-year follow-up period. No significant change in wall stress was observed.

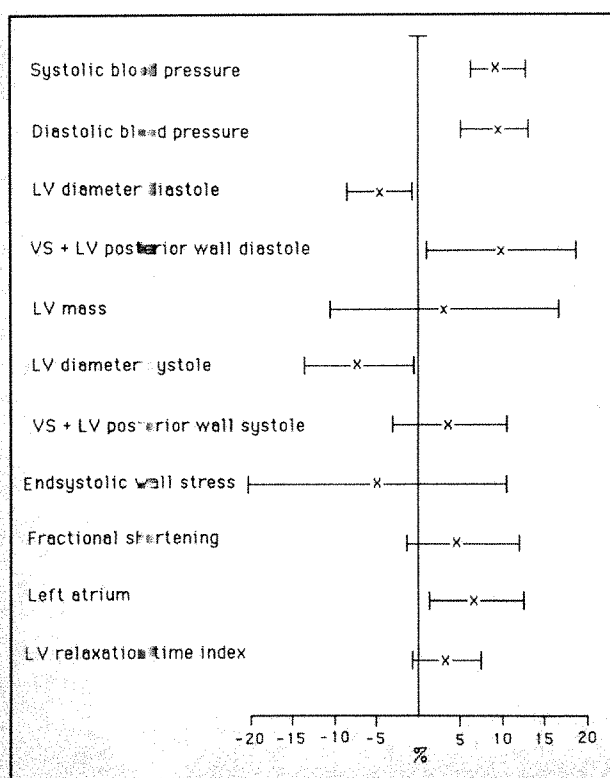


FIGURE 1. Blood pressure, left ventricular (LV) morphology and function. Mean changes during a 4-year period (%), and 95% confidence intervals. VS = ventricular septal.

The results of this investigation showed significant increases in systolic and diastolic blood pressures during the 4-year follow-up period. LV wall thickness increased significantly during the 4-year follow-up period, as well. Concomitant signs of reduced LV distensibility were recorded as indicated by a decrease in LV end-diastolic diameter and an increase in left atrial size. There were no signs of any change in LV systolic pump function.

The high prevalence of cardiovascular and other diseases among elderly subjects implies certain difficulties in defining healthy study groups. Two representative samples, including 768 subjects at age 75 and 404 at age 81, made it possible for us to find a group of healthy subjects for a longitudinal study. Strict inclusion criteria were used to define the group as healthy. The aim of the investigation was to study LV function in healthy elderly people during 4 years of physiological aging. Subjects with signs or symptoms of disease occurring during the follow-up period were consequently excluded. The lack of sex differences at high ages made possible the pooling of men and women in the statistical analysis of longitudinal changes after age 75.

Our results, indicating that aging of the heart in healthy people in this age group mainly affects LV diastolic function and not LV systolic function, accord well with results from cross-sectional studies.^{1-6,13} Several studies using Doppler echocardiography have shown a slowing of the peak velocity of rapid mitral inflow with age and an age-related increase in mitral inflow velocity during atrial contraction.

The increases in systolic and diastolic blood pressures, especially in subjects aged 81 to 85 years, are interesting, however, since earlier studies have shown decreases in systolic and diastolic blood pressures after age 75.^{14,15} Longitudinal data up to age 85 from our study group show that the decrease in systolic blood pressure begins later and is less pronounced in subjects without disease (unpublished data). It seems possible that a subgroup of "healthy" subjects in our study at the age of 85 have not reached the point when blood pressure starts to decrease.

The question arises: What is the explanation for the increase in wall thickness recorded during follow-up? One possibility is an increase in wall thickness due to an increase in afterload, but in such a case it is likely that an increase in LV mass would have been recorded. We did not observe any increase in LV mass. Another explanation might be an increase in wall thickness secondary to an increased stiffness of the left ventricle. It has been shown that structural changes in the heart, related to aging, are characterized by fibrosis and an increase in collagenous tissue.^{13,15} An acceleration of these degenerative changes in the heart probably also occurs in these subjects without symptoms of disease. The degenerative structural changes will probably increase the stiffness of the LV wall. We did not measure LV filling pressure, but

if filling pressures don't increase, then LV end-diastolic diameter will decrease somewhat and wall thickness will increase accordingly without any change in LV mass, such as we observed. Consequently, we speculate that the increased LV wall thickness is secondary to degenerative changes rather than to increased afterload. The well-preserved systolic LV function may support this hypothesis. Another finding supporting this interpretation is that there was no relationship between changes in blood pressure and changes in LV wall thickness. The increase in left atrial size is probably a sign of decreased LV distensibility. Further prospective studies using noninvasive techniques in larger groups and with a longer follow-up period are warranted to study aging of the heart and the cardiovascular system.

The diastolic dysfunction related to normal aging must be taken into consideration in the medical management of elderly patients with cardiovascular disease. Better diagnostic criteria are needed to optimize drug treatment in patients with symptoms of LV dysfunction. A more strict attitude toward the use of digitalis and diuretics might be advisable in patients with dyspnea on exertion secondary to filling problems of the left ventricle rather than to decreased LV contractility.

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Influence of Doppler Sample Volume Location on Ventricular Filling Velocities

Warwick M. Jaffe, MBChB, Timothy A. Dewhurst, MD, Catherine M. Otto, MD, and Alan S. Pearlman, MD

The ratio of peak early diastolic (E) and peak late diastolic (A) velocities, measured from the Doppler mitral waveform, has been used widely to assess left ventricular diastolic function.¹⁻¹⁰ This ratio is also affected by age,^{2,11} heart rate¹² and loading conditions.^{4,6,9} In some studies, Doppler waveforms have been recorded by sampling at the mitral anulus,¹⁻⁴ in others the sample volume has been placed between the free margins of the mitral leaflets,⁵⁻⁷ and in some the measurement site has not been clearly defined.⁸⁻¹⁰ There is no consensus regarding the optimal position. In the present study we measured E/A ratio at both the mitral tips and anulus in 300 consecutive patients to determine if sample volume location had an important influence.

The study group consisted of 300 consecutive adult patients who met entry criteria during a 6-month period. Of 779 patients referred for echocardiographic evaluation, 479 (61%) were excluded because of mitral stenosis (6%), mitral valve prosthesis (3%), arrhythmia (7%), lack of E/A separation due to tachycardia (16%), technically inadequate Doppler waveforms (9%), failure to record Doppler data at both anulus and leaflet tips (10%), and limited study with no Doppler performed (10%). In each patient, age, sex and clinical diagnosis were noted.

Mitral waveforms were recorded by pulsed Doppler, generally using an Advanced Technology Laboratories instrument (model 600, UM6, UM8 or UM9). In a few patients an Acuson (model 128) or Hewlett-Packard (model 77020) instrument was used. A 5-mm sample volume was positioned first between the mitral leaflets at their free margins and then at the mitral anulus level. Recordings were taken during quiet respiration and stored on videotape. Beats showing the highest E and A velocities were recorded.

Measurements were made using an off-line computer system (Nova MicroSonics, Indianapolis, Indiana). E and A velocities were measured (Figure 1). Doppler measurements were made at the darkest out-

er portion of the velocity waveform in beats showing the least spectral dispersion. At each site, 3 beats were measured. Measurements were made without knowledge of clinical or other echocardiographic findings.

Another independent observer prospectively assessed each echocardiogram and used standard methods to determine: (1) ventricular septal and posterior wall thickness at end-diastole; (2) segmental wall motion abnormalities (present or absent); (3) global left ventricular systolic function (normal, mildly reduced, moderately reduced and severely reduced); (4) severity of valvular regurgitation (0 to 4+); (5) presence and severity of aortic stenosis; and (6) other echocardiographic abnormalities.

Based on the clinical and echocardiographic data, a subset of 56 normal patients was identified. In these patients, echocardiography had been performed to rule out a source of embolus, to evaluate syncope or

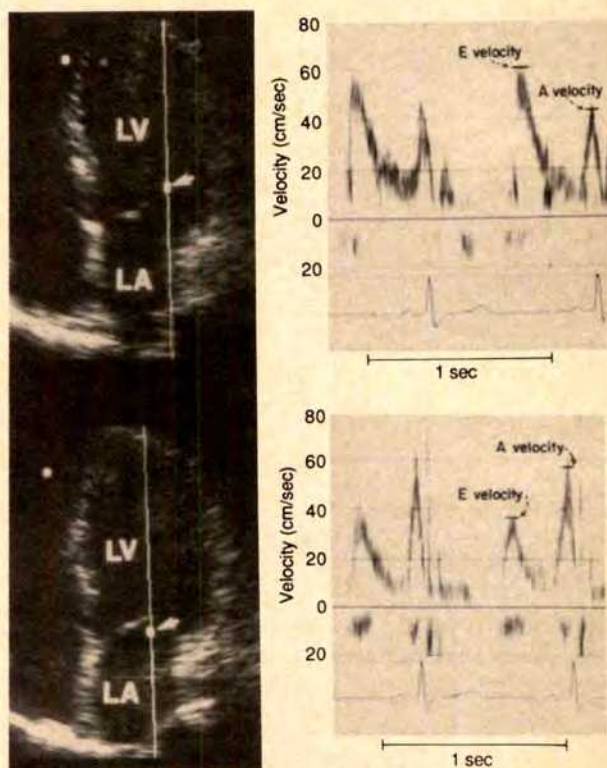


FIGURE 1. Sample volume location and Doppler recordings at mitral leaflet tips (top panel) and anulus (bottom panel). Flow velocity is displayed on vertical axis and time on horizontal axis. A = peak velocity in late diastole; E = peak velocity in early diastole; LA = left atrium; LV = left ventricle.

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palpitations, or to look for vegetations in patients with fever. These 56 patients had no clinical evidence of cardiac disease, and their chest x-rays, electrocardiograms and echocardiograms were normal.

All data were expressed as mean \pm standard deviation. Standard linear regression was used to measure intra- and interobserver agreement, as well as the strength of the relation between measures at the mitral leaflet tips and anulus for E and A velocities, and E/A ratio. Student's paired t test was used to compare mean values.

In 30 randomly selected subjects, mitral waveforms selected by the primary observer were remeasured independently by the same observer and also by a second, blinded observer. Intraobserver variability was minimal; for the repeated observations, mean E/A ratio was 1.31 ± 0.51 vs 1.32 ± 0.53 ($p = \text{not significant}$) and the maximal difference was 0.18. The r value for this relation was 0.99. Interobserver vari-

TABLE 1 Patient Data

Parameter	Group 1	Group 2
No. of patients	300	56
Age (years)	56 ± 19	40 ± 13
Heart rate (beats/min)	69 ± 13	65 ± 11
E velocity tips (cm/s)	75 ± 22	72 ± 14
E velocity anulus (cm/s)	45 ± 15	48 ± 12
A velocity tips (cm/s)	64 ± 28	47 ± 14
A velocity anulus (cm/s)	47 ± 14	42 ± 10
E/A ratio tips	1.36 ± 0.65	1.63 ± 0.53
E/A ratio anulus	1.05 ± 0.52	1.21 ± 0.42

Values (for age, heart rate and Doppler measures) are mean \pm 1 standard deviation.

A = peak late diastolic velocity; E = peak early diastolic velocity; Group 1 = entire series; Group 2 = patients without heart disease.

ability was also small. Mean E/A ratio was 1.31 ± 0.51 for observer 1 vs 1.30 ± 0.54 for observer 2 ($p = \text{not significant}$). The maximal difference was 0.35. The r value for this relation was 0.98.

Table 1 summarizes the data from the 300 patients. There were 162 men and 138 women, aged 18 to 92 years. Mean E velocity was 75 cm/s at the mitral leaflet tips versus 45 cm/s at the anulus ($p < 0.001$). Figure 2 shows a statistically significant relation between E velocities at the tips and at the anulus ($y = 0.4x + 14.8$, $r = 0.60$, standard error of the estimate [SEE] 17.4 cm/s). Mean A velocity was 64 cm/s at the tips versus 47 cm/s at the anulus ($p < 0.001$). Figure 2 also shows a statistically significant relation between A velocities at the tips and at the anulus ($y = 0.4x + 23.7$, $r = 0.71$, SEE = 19.5 cm/s). Nonetheless, mean E/A ratio at the tips was higher than at the anulus (1.36 vs 1.05 , $p < 0.001$). Figure 3 shows the relation between E/A ratio at the tips and at the anulus ($y = 0.6x + 0.2$, $r = 0.80$, SEE = 0.39).

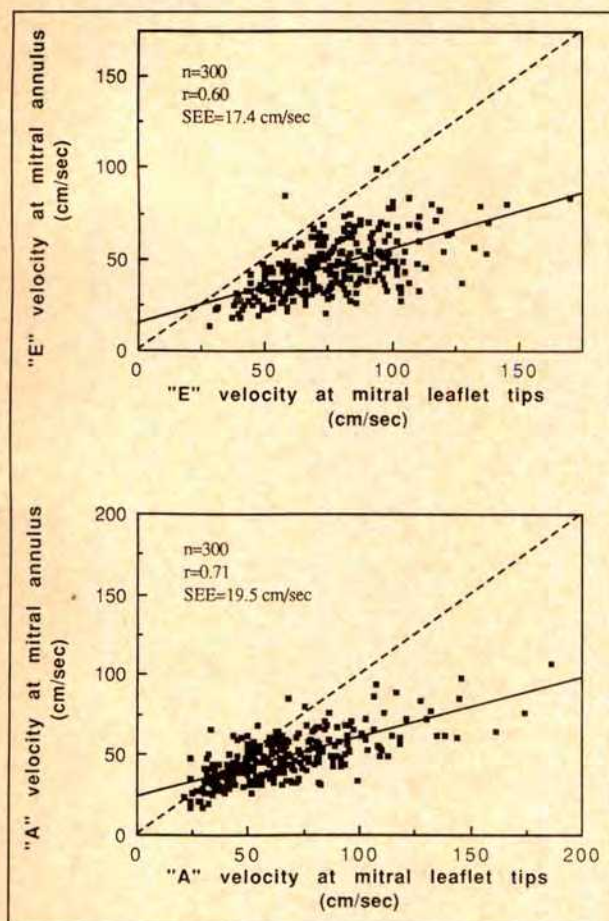


FIGURE 2. Peak velocity at mitral leaflet tips (horizontal axis) is plotted against peak velocity at mitral anulus (vertical axis). Early diastolic ("E") velocity is shown in top panel, and late diastolic ("A") velocity is shown in lower panel. Dashed line is line of identity and solid line is regression line. In both cases, most points are below line of identity. SEE = standard error of the estimate.

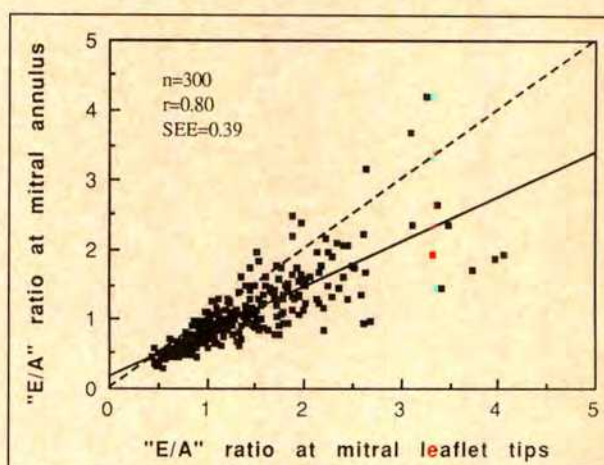


FIGURE 3. Peak early to peak late diastolic velocity ("E/A") ratio at mitral leaflet tips (horizontal axis) is plotted against E/A ratio at mitral anulus (vertical axis). Most points are below line of identity (dashed line), and scatter of data increases with absolute value of E/A ratio. SEE = standard error of estimate.

There was significant scatter of the data, particularly at higher E/A ratios. Results were similar when only normal subjects were considered: mean values for E and for E/A ratio both were significantly higher at the tips than at the anulus ($p < 0.001$), as was the A velocity ($p = 0.03$).

This report shows that the E/A ratio can be different when measured at the mitral leaflet tips and at the mitral anulus. In some patients, these differences are substantial. E velocity generally is higher at the tips than at the anulus, whereas A velocity also is higher, but by a relatively smaller amount. Thus, E/A ratio measured at the anulus is usually lower than at the tips.

One previous study¹³ compared mitral waveforms measured at 2 different sites (low in the left atrium cephalad to the mitral anulus, and at the level of the mitral valve between the anulus and leaflet tips) in 40 normal subjects. Although the directional changes in E and A velocities were similar to those found in this study, there was no significant difference between mean A/E ratios at the 2 sites. The small number of patients evaluated, lack of abnormal findings and differences in sampling sites may account for some of the numerical discrepancies between the 2 studies.

Mitral diastolic velocities should be recorded with pulsed Doppler, and anatomic landmarks should be used to establish the site of sampling. Serial studies in the same person should use the same sampling site and should indicate the sampling site, because absolute values for E and A velocities and E/A ratios may differ significantly with sample volume placement.

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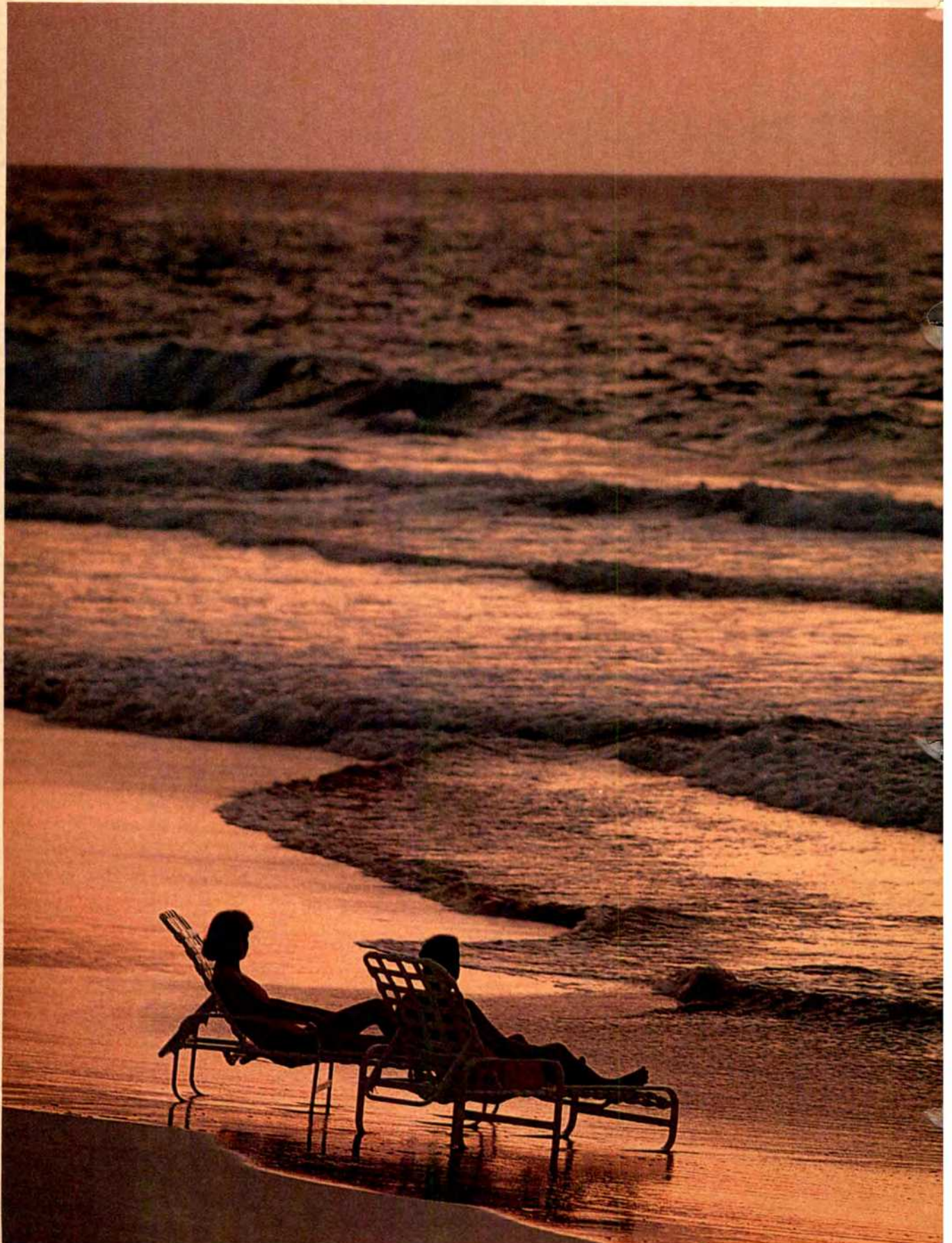
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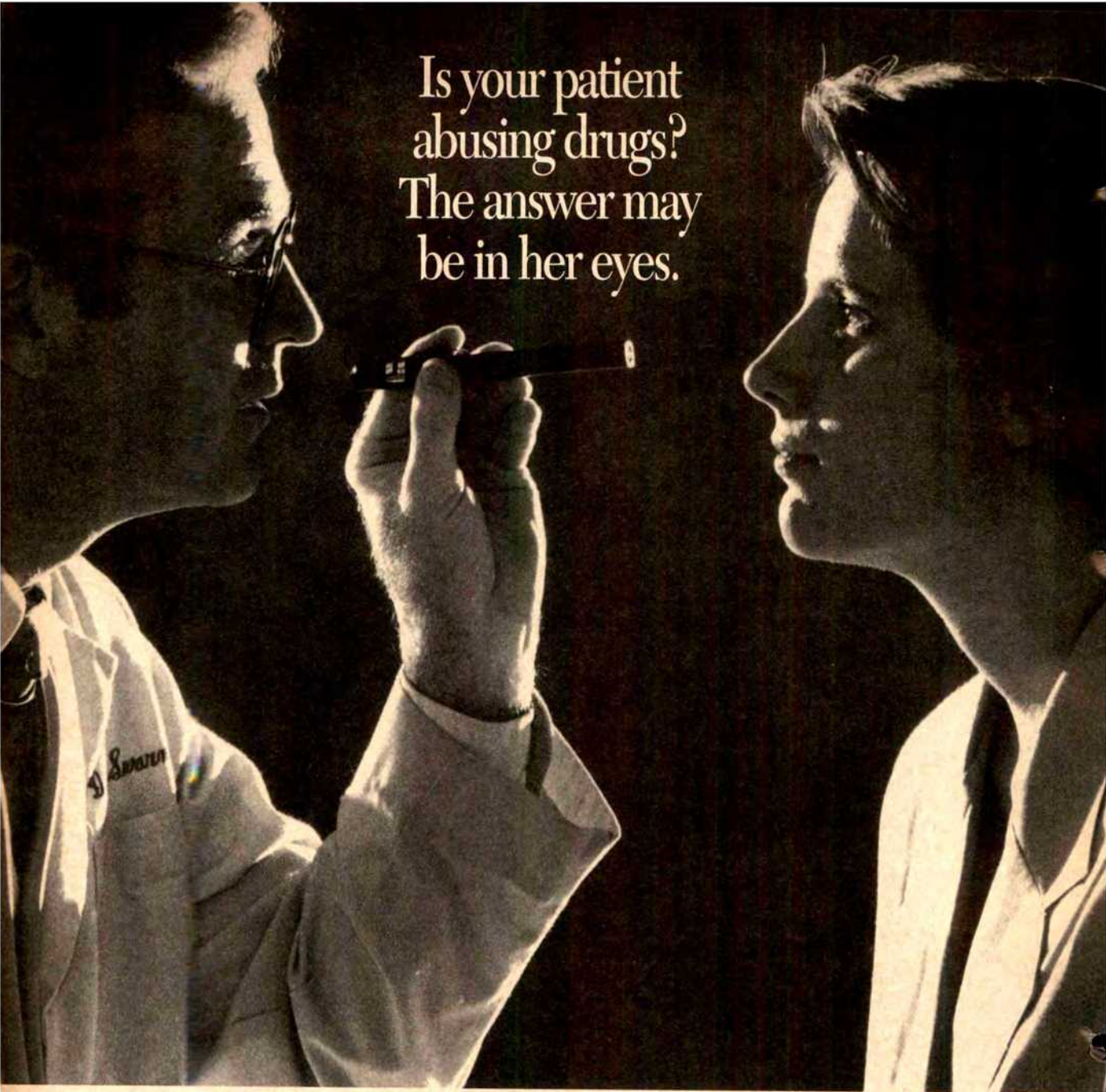
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Independent Effects of Low Frequency Magnitude and Phase Distortion on the Recorded Electrocardiogram

Ted J. Dustman, ME, Marc S. Fuller, PhD, and Sally Sharp, MD

Electrocardiographic signals must go through electronic amplification and filtering to increase amplitude and to diminish noise before they are recorded. However, amplification and filtering may introduce unwanted magnitude and phase distortion in the recorded signal. The relative importance of inadequate magnitude versus inadequate phase responses of electrocardiographic recording systems has been a subject of debate. Although electrocardiographic signal distortion due to inadequate magnitude response has been identified,¹ there is evidence^{2,3} that phase distortion has a greater effect on clinical interpretation of the recorded electrocardiogram.

This study was designed to quantify the independent effects of low-frequency magnitude and phase distortion on electrocardiographic signals. Electrocardiographic signals from Holter recordings in 10 patients were digitized and processed by magnitude-modifying and phase-modifying filters. The independent effects of magnitude and phase distortion were evaluated by calculating cross-correlation coefficients between filtered and unfiltered waveforms in each patient.

The study group consisted of 10 adult patients with angina pectoris who were scheduled to undergo either diagnostic coronary arteriography or an exercise treadmill test at the University of Utah. Holter recordings were performed during both procedures using 2 bipolar leads attached to either a DelMar model 456A cassette recorder or a Cardiodata C-60 cassette recorder. The recording leads were attached to electrodes in the V_2 - V_3 position and in an inferolateral V_5 -like position. Subsequent processing used the signal from the V_5 lead only.

Holter recordings were played back to an IBM PC using a Personal Computers for Medicine Holter cassette playback machine. The frequency response of the recording and playback system was measured to insure proper signal reproduction. The analog recording from each Holter tape was digitized with 12-bit accuracy and the digitized data were saved to disk. The effective sampling rate was 100 Hz. For each patient, a normal sinus beat was extracted from the digitized data file for analysis. To study the independent effects of magnitude and phase distortion, the digitized sinus beats were then processed by 2 types of filters.

To study the effects of magnitude distortion, we developed 3 finite impulse-response high-pass filters. The Fourier transform method with a Kaiser window function was used for the design of the filters.⁴ Figure 1 shows the magnitude response of these filters.

These filters delay all frequencies equally. This means that a signal processed by the filter will not be distorted by changes in phase, but will be distorted by changes in the magnitudes of the frequency components. High-pass filters suppress frequencies below the "cutoff" frequency. Cutoff frequencies of the fil-

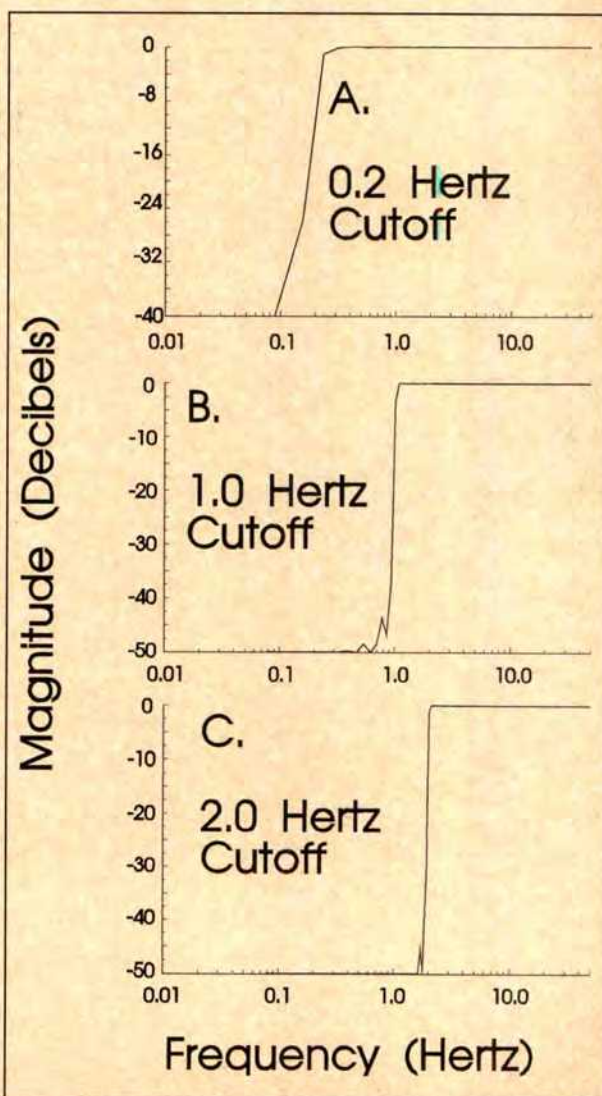


FIGURE 1. Magnitude response of finite impulse-response filters. **A.**, magnitude response of filter with cutoff frequency at 0.2 Hz. **B.**, magnitude response of filter with cutoff frequency at 1.0 Hz. **C.**, magnitude response of filter with cutoff frequency at 2.0 Hz.

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TABLE I Cross-Correlation Coefficients for Each Patient and Filter

	Patient Number										Mean \pm SD
	1	2	3	4	5	6	7	8	9	10	
All-pass (0.2 Hz)	0.898	0.776	0.927	0.712	0.939	0.992	0.989	0.466	0.707	0.888	0.829 \pm 0.165
All-pass (1.0 Hz)	0.578	0.745	0.586	0.849	0.859	0.799	0.663	0.451	0.407	0.726	0.666 \pm 0.158
All-pass (2.0 Hz)	0.227	0.681	0.643	0.688	0.624	0.559	0.405	0.153	0.151	0.353	0.448 \pm 0.218
FIR (0.2 Hz)	1.000	1.000	0.986	1.000	0.997	1.000	1.000	1.000	0.999	1.000	0.998 \pm 0.004
FIR (1.0 Hz)	1.000	0.991	0.953	0.999	0.996	1.000	0.991	0.981	0.999	1.000	0.991 \pm 0.015
FIR (2.0 Hz)	0.859	0.937	0.932	0.973	0.985	0.977	0.980	0.877	0.800	0.946	0.927 \pm 0.062

FIR = finite impulse response; SD = standard deviation.

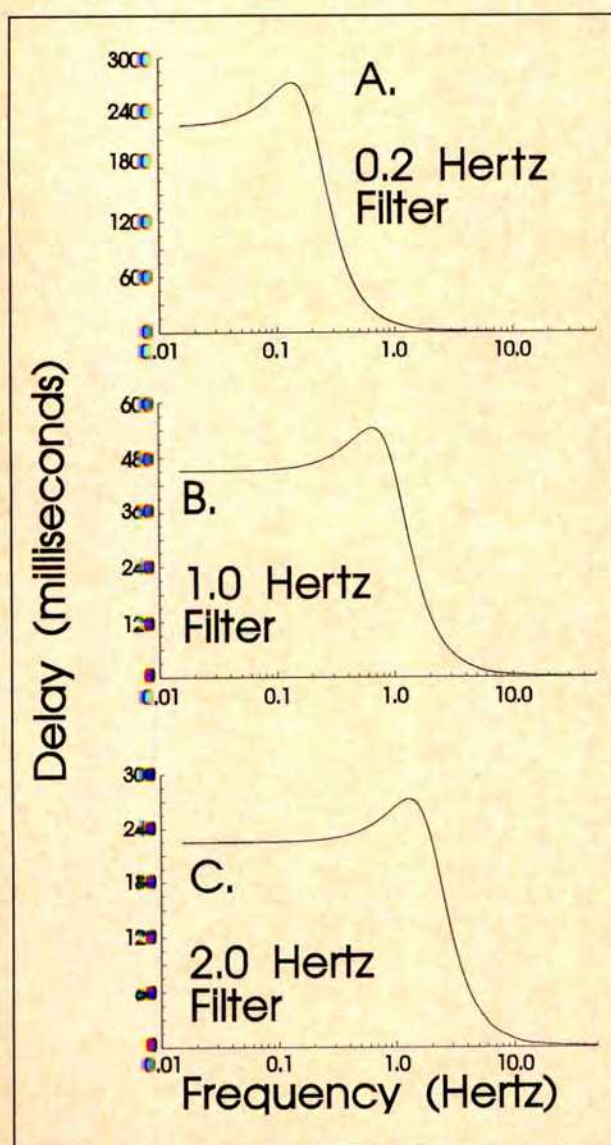


FIGURE 2. Time delay curves for each all-pass filter. **A.**, filter induces maximal delay near 0.2 Hz. **B.**, filter induces maximal delay near 1.0 Hz. **C.**, filter induces maximal delay near 2.0 Hz. Filter inducing no phase distortion would produce same time delay at all frequencies, i.e., time delay curve would be horizontal line.

ters used in this study were 0.2, 1.0 and 2.0 Hz, respectively.

To study the effects of phase distortion we developed 3 all-pass infinite impulse-response filters. All-pass filters have a unity magnitude response at all frequencies and they distort signals by changing phase relationships only. We designed three 2-pole all-pass filters with phase responses similar to fourth-order Butterworth filters. Butterworth filters are commonly used in electrocardiographic recording equipment and induce undesirable phase distortion. The all-pass filters we developed induced maximal phase distortion (delay) near the frequencies 0.2, 1.0 and 2.0 Hz, respectively. Figure 2 shows the time delay at each frequency for these filters.

The effects of magnitude and phase distortion were quantified by comparing an unfiltered waveform with its filtered counterparts. The normal sinus beat of each patient was processed by the 3 finite impulse-response filters and by the 3 all-pass filters. Each of the resulting 6 waveforms were compared with the unfiltered sinus beat to evaluate the distortion introduced by each filter.

For each patient, a cross-correlation coefficient was computed between the sinus beat and the 6 filtered versions of the sinus beat. The cross-correlation coefficient is given by⁵:

$$R = \frac{\sum_{i=1}^n x_i y_i}{\sqrt{\sum_{i=1}^n x_i^2} \sqrt{\sum_{i=1}^n y_i^2}}$$

where x and y are the waveform vectors to be correlated.

Cross-correlation coefficients range from -1 to 1 . A value of 1 indicates that the 2 waveforms being compared are identical, a value of 0 indicates that

they are uncorrelated and a value of -1 indicates that they are mirror images of each other. The value of the cross-correlation coefficient at which waveforms can be considered different depends on the nature of the waveforms and the purpose of the study. We chose a high value (0.98) that will discriminate small differences in waveforms, but not be so high that differences may be due to computational round-off errors.

Table I shows the cross-correlation coefficients between the unfiltered waveform and the 6 filtered waveforms for each patient. Figure 3 displays the

original waveform and its 6 filtered counterparts for 4 patients.

No change was induced by the 0.2-Hz finite impulse-response filter. The 1.0-Hz finite impulse-response filter induced a significant change in only 1 patient. The 2.0-Hz finite impulse-response filter induced changes in most patients and values for the cross-correlation coefficients ranged from 0.80 to 0.98.

The phase distortion (all-pass) filters altered the electrocardiographic signals in the following ways:

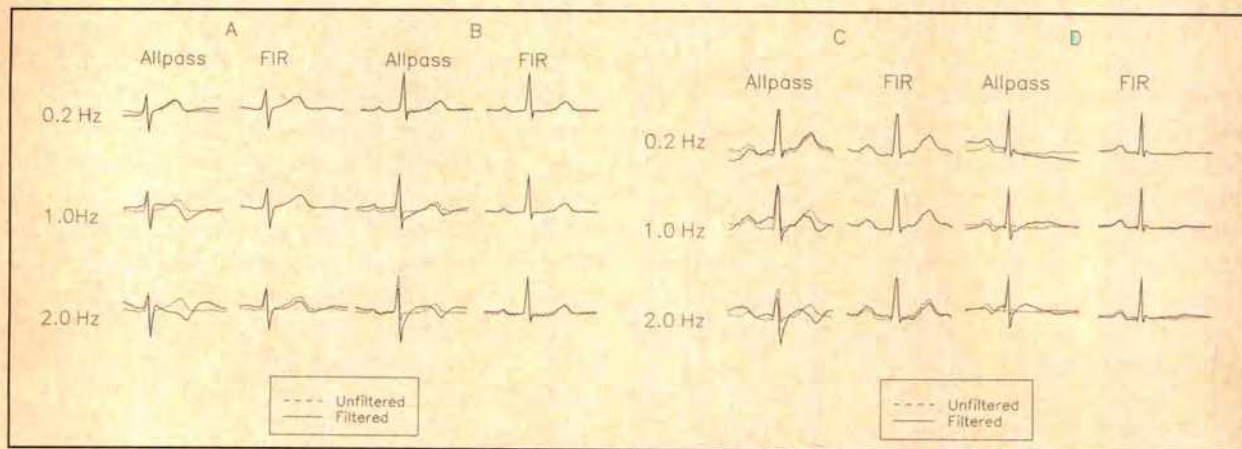


FIGURE 3. Morphologic changes produced by filters in electrocardiograms of 4 patients. Dashed lines are unfiltered beats; solid lines are filtered beats. Some filters produced no changes; in these cases, only solid line appears. A, changes produced in subject 1. B, changes produced in subject 7. C, changes produced in subject 10. D, changes produced in subject 2. FIR = finite impulse-response filter.

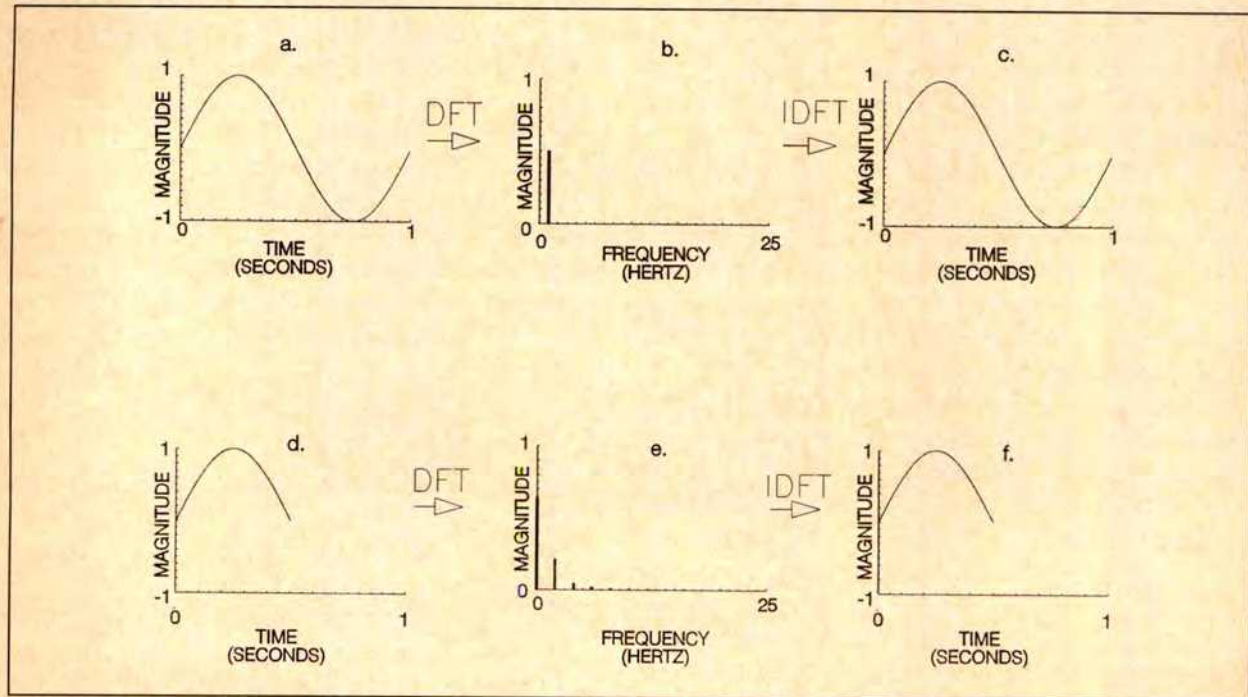


FIGURE 4. Demonstration that no filtering is performed when discrete Fourier transform (DFT) is followed by inverse discrete Fourier transform (IDFT). a., 1 cycle of 1-Hz sine wave; 1,000 points sampled at 1,000 Hz to produce figure. b., frequency representation of sine wave (derived via DFT); all energy concentrated at 1 Hz. c. was produced by applying IDFT to frequency spectrum. Waveform completely restored by IDFT. d., $\frac{1}{2}$ cycle of 1-Hz sine wave. Waveform created by sampling 1-Hz sine wave at 2,000 Hz for $\frac{1}{2}$ second, producing 1,000 points, as before. e., frequency spectrum of waveform obtained via DFT; fundamental frequency of spectrum is 2 Hz. f. was produced by applying IDFT to spectrum. Half-cycle waveform is restored, demonstrating that DFT followed by IDFT performs no filtering.

The 0.2-Hz all-pass filter induced a low-frequency drift (drift was not removed before computing cross-correlation coefficients and so the low correlation coefficients may reflect the slope of filtered signals compared with that of unfiltered signals). The 1.0- and 2.0-Hz all-pass filters changed the sinus waveform significantly for all patients, although the morphologic changes that were produced varied. In some patients there was elevation of the ST segment, whereas in others the ST segment was depressed. In some patients the T wave was delayed and inverted. In many patients the QRS complex was altered.

In this study we have demonstrated that inadequate low-frequency phase response has significantly greater effect on accurate reproduction of morphology than does inadequate low-frequency amplitude response. Amplitude distortions ≤ 1 Hz do not appear to alter electrocardiograms significantly, whereas phase distortion at frequencies as low as 0.2 Hz result in significant changes in the electrocardiographic waveform. This is especially important with regard to the ST segment because several of the distortions resemble morphologies attributable to myocardial ischemia.

There has been controversy regarding the optimal low-frequency response necessary to reproduce the ST segment accurately. Balasubramanian et al⁶ reported that ST-segment distortion was caused by poor low-frequency amplitude response. However, results reported by Bragg-Renschel et al¹ suggest that extended low-frequency response capabilities are not necessary to accurately reproduce electrocardiographic signals. The adequacy of phase response of the recording system used was not considered in either of these 2 studies.^{1,6}

In another study, Lambert et al⁷ attempted to examine the effects of inadequate low-frequency magnitude response without introducing phase distortion. They concluded that removing frequencies as high as 2.0 Hz did not introduce any significant distortion in electrocardiographic signals. However, the filtering technique used in their study did not alter the electrocardiogram. Lambert et al used the forward discrete Fourier transform and the inverse discrete Fourier transform in combination with 3 sampling rates in an attempt to filter low frequencies from the electrocardiogram. An electrocardiogram was sampled at rates of 200, 1,000 and 2,000 Hz. At each rate, 1,024 samples were digitized, producing waveforms with fundamental frequencies of 0.2, 0.98 and 1.95 Hz, respectively. Apparently, these investigators incorrectly believed that the sampled waveforms contained frequencies below their fundamental. The frequency spectrum produced by the forward transform, of course, did not contain frequencies below the fundamental (except for the direct current component). The forward and inverse transforms were then applied in an attempt to construct waveforms lacking frequency components below the fun-

damental. However, the combination of the forward and inverse transforms did not change the waveforms. The forward transform followed by the inverse transform, with no intervening processing, will always reproduce the original waveform. Thus, there were no differences between the "filtered" and unfiltered waveforms. Figure 4 illustrates this discussion. In this example, we sample 1,000 points of a sine wave at 1,000 Hz and again at 2,000 Hz, and compute the discrete Fourier transform and inverse discrete Fourier transform of each sampled waveform. In each case, no distortion is induced by the procedure.

Taylor and Vincent^{2,3} induced phase distortions without introducing magnitude distortion in electrocardiograms using an analog all-pass network to delay selected frequencies. The ST-segment changes they induced mimic those produced by myocardial ischemia. They concluded that an ideal electrocardiographic recording system should have a linear phase response from 0.5 to 75 Hz. Our results agree qualitatively with these results. In addition, we have demonstrated other effects of phase distortion including low-frequency drift, ST-segment depression and alteration of the QRS complex. We have also quantified the differences between filtered and unfiltered electrocardiograms by calculating cross-correlation coefficients. Clearly, linear phase response extending to ≥ 0.2 Hz is required to avoid these undesirable distortions.

In conclusion, a reexamination of the American Heart Association standards for surface electrocardiographic monitoring is needed. New standards⁸ for phase response (linear to 0.05 Hz) are necessary. However, amplitude response < 1.0 Hz is not needed, and may even be detrimental because baseline drift typically occurs in the range of 0.1 to 2.0 Hz. Magnitude and phase responses have previously been evaluated jointly because it is difficult in analog design to measure independent responses. However, as we have shown, with digital signal processing, these 2 types of distortion can and should be considered independently to ensure signal fidelity.

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Validation of a Bedside Method of Activated Partial Thromboplastin Time Measurement with Clinical Range Guidelines

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Rapid measurement of an anticoagulant effect due to heparin is desirable in a variety of settings. Patients with cardiovascular diseases undergo heparinization for many reasons including management of unstable angina, in conjunction with thrombolytic therapy for myocardial infarction, percutaneous transluminal coronary angioplasty, extracorporeal bypass, atrial fibrillation with perceived embolic risk, prosthetic heart valves and several variants of cerebral vascular disease.¹⁻⁹ Standard clinical laboratory measurements of partial thromboplastin time (PTT) are cumbersome and slow, and prone to multiple potential sources of error.^{2-4,10-13} To provide a rapid, simple, accurate bedside means of PTT measurement, the Hemochron system was used to assess a means of automated immediate analysis. We assessed the utility of this system in the cardiac catheterization laboratory by comparing PTT measurements derived from this technique with activated

clotting times (ACT) in patients undergoing cardiac catheterization and angioplasty both before and after the procedure.

The study group consisted of 176 patients undergoing cardiac catheterization or coronary angioplasty. Baseline (0 heparin) PTT and ACT measurements were obtained immediately after vascular access of the femoral artery and placement of an 8Fr catheter introducer sheath. Blood samples were obtained after 5-ml backflush of blood. Of the patients undergoing cardiac catheterization, 51 received 2,000 U of heparin intravenously after vascular access was achieved at the discretion of the catheterizing physi-

TABLE 1 Measured Laboratory Values for Heparin Groups

	Heparin (U)		
	0	2,000	10,000
No. of pts.	176	51	65
PTT (sec)	67 ± 14	153 ± 74	480 ± 150
ACT (sec)	119 ± 21	184 ± 64	460 ± 141

Values are means ± 1 standard deviation.
ACT = activated clotting time; PTT = activated partial thromboplastin time.

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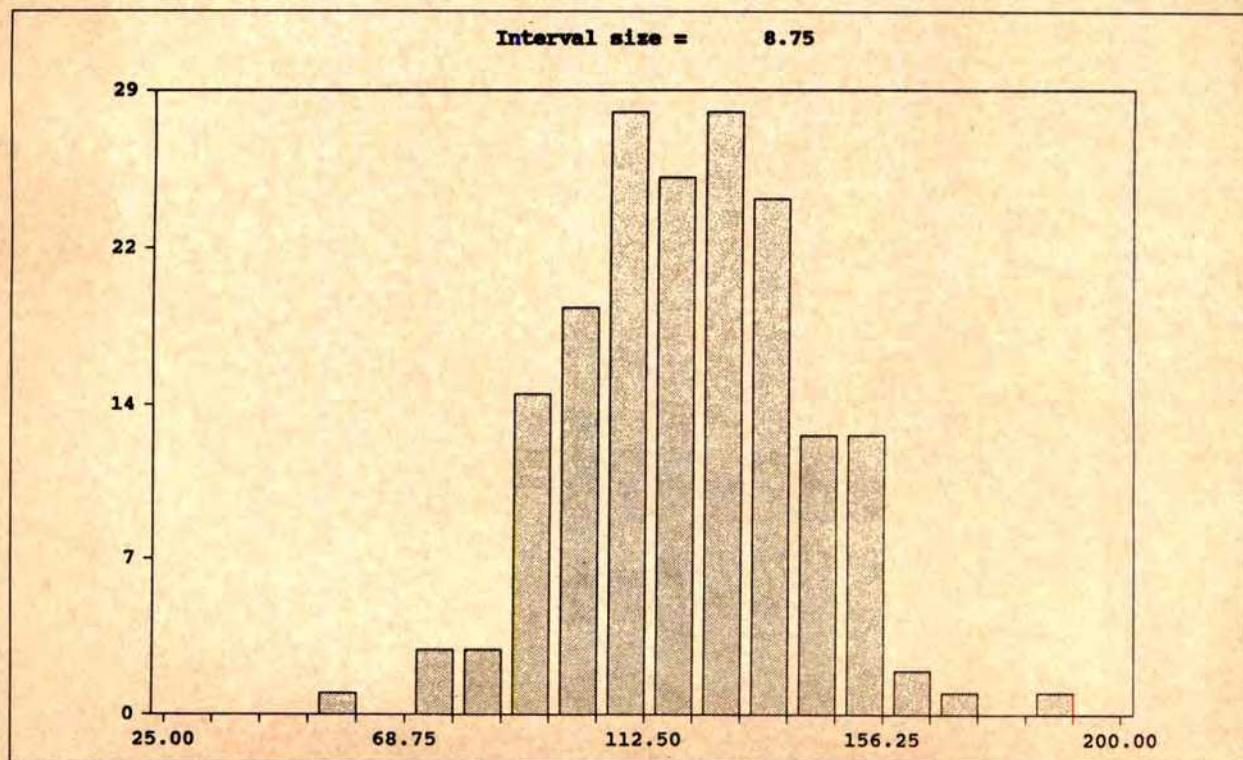


FIGURE 1. Distribution of activated clotting times in 0 heparin group (follows normal distribution).

cian. All the patients who underwent coronary angioplasty received 10,000 U after vascular access. In the patients who received heparin, repeat ACT and PTT measurements were obtained at the conclusion of the procedure to address the effects of heparin on anticoagulant parameters. Cardiac catheterization and angioplasty were performed via standard femoral technique using 2Fr diagnostic and guide configurations and a variety of over-the-wire balloon angioplasty

systems. Dextran was not used in any patient, nor was any patient receiving heparin or coumadin before the study. Most patients undergoing diagnostic catheterization and all undergoing angioplasty were receiving aspirin, 325 mg/day.

The heparin administered throughout the duration of the study was porcine heparin (LyphoMed, Inc., Melrose Park, Illinois). ACTs and activated PTTs were measured in the catheterization laboratory, us-

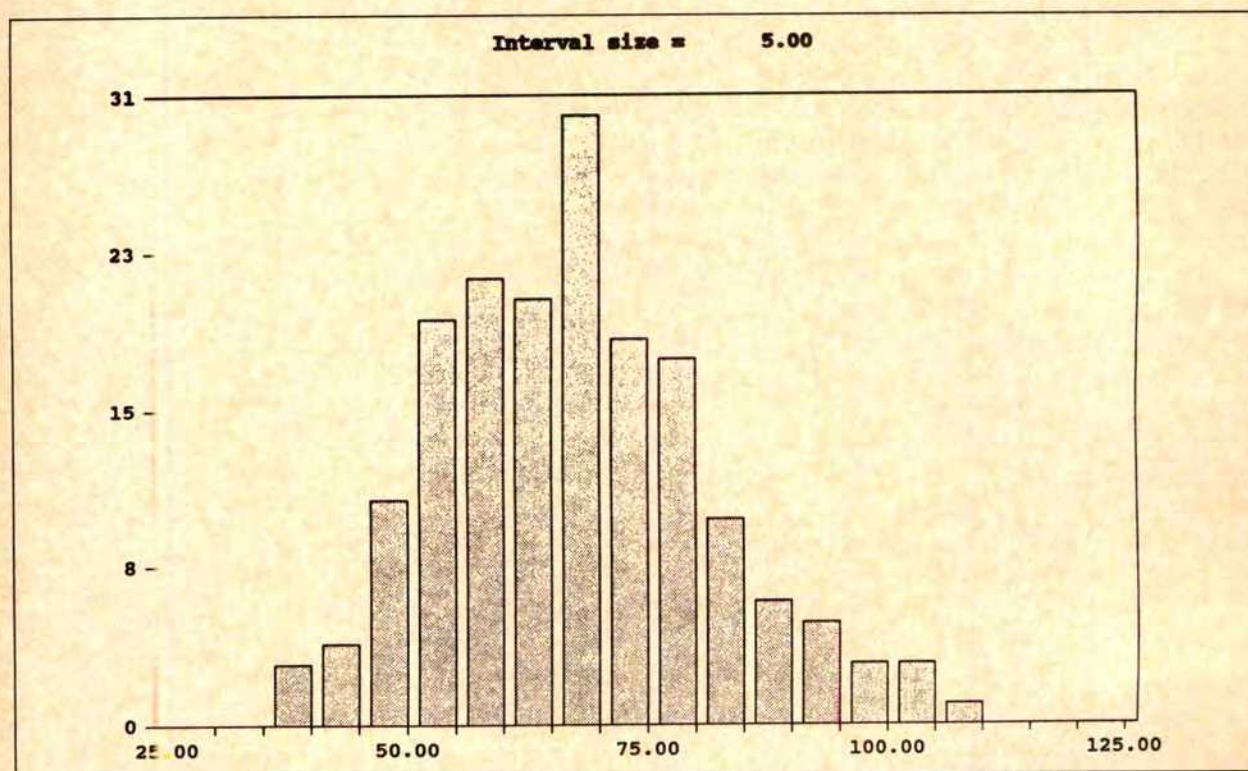


FIGURE 2. Distribution of partial thromboplastin times in 0 heparin group (follows normal distribution).

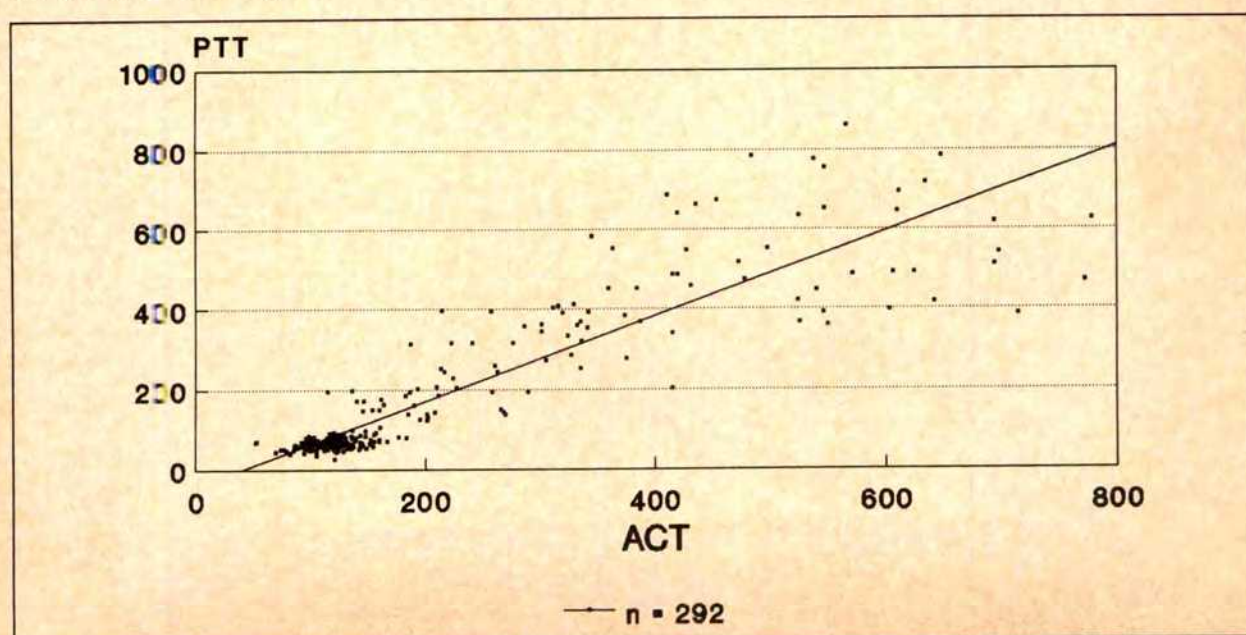


FIGURE 3. Plot of partial thromboplastin time (PTT) versus activated clotting time (ACT) for all values (linear correlation).

ing the materials of the Hemochron system (International Technidyne Inc., Edison, New Jersey). The Hemochron 800 assay device was used in conjunction with A101 test tubes for PTT measurement. The tubes contain pre-prepared lyophilized sodium citrate, diatomaceous earth activator, platelet factor substitute, stabilizers and buffers and are combined with 1.0 ml of calcium chloride (0.032 M). This method utilizes fresh whole blood and has been demonstrated to result in PTT measurements that are reproducible and correlate well with standard clinical laboratory methods. However, the values obtained with this method are higher than those obtained through standard clinical laboratory techniques. Mean PTT in a normal population is 70 seconds (standard deviation 7.3, range 55 to 85, noted in the product literature). ACTs were also measured using the Hemochron 800 instrument, with FTCA510 tubes that are celite-activated (12 mg Johns Manville celite diatomaceous earth). This method has been shown to be a reliable and reproducible means of measuring activated coagulation times in a variety of settings.^{2,5,7,9,14-17} Both ACT and PTT results are routinely available within 5 to 10 minutes of blood drawing.

Statistical analysis included calculations of mean ± 1 standard deviation, Pearson product moment correlation, best curve fit analysis, and standard calculation of sensitivity, specificity, accuracy and predictive values.

Table I lists the number of data points reflecting the effects of 0, 2000, or 10,000 U of heparin with accompanying descriptive statistics. The ACT and PTT values obtained showing 0 heparin effect follow normal distributions (Figures 1 and 2). Overall correlation between PTT and ACT was excellent ($r = 0.902$ by linear correlation [$PTT = (1.066 \times ACT) - 45.936$] and $r = 0.925$ by power function [$\ln PTT = [1.333 \times \ln ACT] - 2.094$]). Figure 3 plots the relation between PTT and ACT by linear analysis. Because as the postheparin measurements were obtained over variable intervals after drug administration, they provide a range of data representing a broad spectrum of anticoagulant effect.

In our laboratory, normal ACT measurements are 129 ± 9 seconds (range of 110 to). Therapeutic ACT is believed to be ≥ 200 seconds during standard anticoagulation.^{2,5,7,9,14-17} For protection during angioplasty we prefer an ACT ≥ 300 seconds to achieve suprathreshold anticoagulant effect.^{5,9,17} By sequential testing, a PTT measurement ≥ 120 seconds was believed to yield optimal sensitivity and specificity for diagnosis of therapeutic standard anticoagulant effect when compared with ACT values. A PTT ≥ 120 seconds, when correlated with an ACT ≥ 200

seconds, resulted in a sensitivity of 99%, a specificity of 93%, an accuracy of 93%, a positive predictive value of 85% and a negative predictive value of 99%.

To assess suprathreshold effect for adequate anticoagulation during angioplasty, a PTT ≥ 300 seconds correlated with an ACT ≥ 300 seconds with sensitivity of 90%, specificity of 97%, positive predictive value 89%, negative predictive value 97%, and accuracy 96%.

The Hemochron system for PTT measurement appears to fulfill many of the requirements for a rapid, simple and reproducible technique. However, to our knowledge, this method has not been validated in a large number of patients undergoing cardiac catheterization. Our study demonstrates the utility of this technique and provides guidelines for its use, including the assessment of a therapeutic anticoagulant effect of heparin used during coronary angioplasty, when "suprathreshold" levels of anticoagulation are desired.

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Cardiac Transplantation for Giant Coronary Artery Aneurysms Complicating Kawasaki Disease

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Coronary artery aneurysm formation is a well-known and widely reported complication of Kawasaki disease with the incidence ranging from 15 to 25%.¹ Most aneurysms are small and, in general, are associated with a favorable prognosis. In contrast, giant aneurysms (>8 mm in diameter) are associated with higher morbidity and mortality, despite antiplatelet and anticoagulation therapy.² Systemic urokinase has been used to treat coronary artery thrombosis of these aneurysms, but with limited success.³ Coronary artery bypass graft surgery currently appears to be the most effective therapy for ongoing ischemia, but serious limitations exist.⁴ Although cardiac transplantation now is used widely to treat a number of lethal cardiac diseases affecting children, this therapeutic approach has not been reported in the management of coronary involvement in Kawasaki disease.

On the eleventh day of an acute febrile illness, a 14-year-old boy was diagnosed to have Kawasaki disease complicated by giant coronary artery aneurysms. Initial inpatient management included high-dose intravenous gamma globulin and heparin, with subsequent conversion to warfarin, low-dose aspirin and dipyridamole for outpatient management. Ten weeks after diagnosis, the patient presented with an acute myocardial infarction. An echocardiogram (Figure 1) revealed extensive

thrombus in the left anterior descending and right coronary arteries.

Intravenous heparin was begun and the patient underwent cardiac catheterization which revealed total occlusion of the aneurysmal proximal right coronary artery, large thrombus within the giant fusiform aneurysm of the left anterior descending coronary artery, extensive aneurysm formation of the circumflex artery (Figure 2, left) and extensive distal coronary stenosis. Tissue plasminogen activator was administered, intravenous heparin was continued and aspirin was begun.

Coronary angiography 24 hours later showed patency of the right coronary artery with extensive residual (Figure 2, right) and persistent thrombi in the left anterior descending artery. A second course of thrombolytic therapy using urokinase was initiated, and coronary angiography after 48 hours revealed little change. Urokinase was discontinued, warfarin

was begun, and the patient subsequently underwent heart transplantation.

Gross pathologic examination of the native heart revealed extensively dilated coronary arteries with thickened walls (Figure 3). The left main coronary artery was aneurysmal with organized thrombus present. The left anterior descending and circumflex arteries were proximally dilated with 65 and 85% distal stenoses, respectively. The right coronary artery had thrombus within a proximal aneurysm and 60 to 90% progressive distal stenosis. Smaller epicardial arteries were severely stenotic.



FIGURE 1. Echocardiogram with arrows showing left anterior descending artery thrombus.

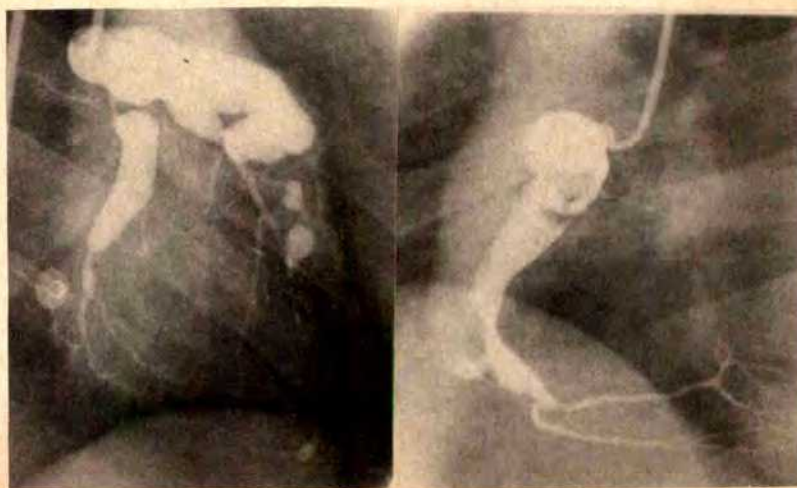


FIGURE 2. Left, arteriogram showing abnormal left anterior descending and circumflex arteries. Right, arteriogram showing abnormal right coronary artery.

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In a study of 42 patients with Kawasaki disease and abnormal coronary arteries, all aneurysms >9 mm in diameter were complicated by subsequent total occlusion.¹ This observation reflects a distinction which is made between typical and giant aneurysms. Typical aneurysms are <8 mm in diameter and generally reflect a less malignant course since they are more likely to regress over time, posing less risk of thrombosis. However, giant coronary artery aneurysms frequently become obstructed or stenotic and develop thrombosis.²

Early administration of intravenous gamma globulin reduces the prevalence of coronary aneurysms.⁵ Coronary artery bypass grafting for proximal stenoses is also an option, but the limited survival of grafts remains a problem.^{4,6} Given the extent of aneurysmal disease, the severity of distal stenosis, and the continuing risk of thrombosis and embolization, bypass grafting was not recommended for our patient.

Whereas most children with Kawasaki disease and giant coronary artery aneurysms can be managed with conservative medical therapy, some patients will develop severe thromboocclusive coronary artery disease. Bypass grafting for proxi-

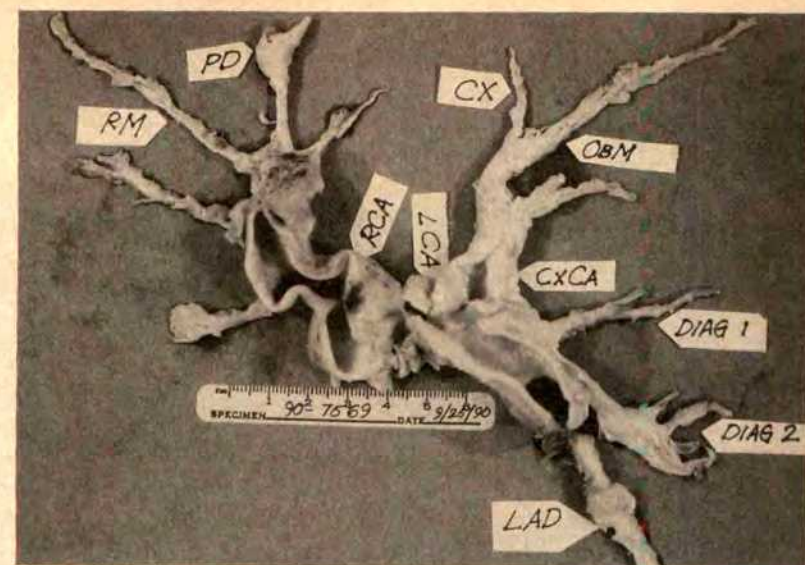


FIGURE 3. Abnormal coronary arteries. CX = circumflex; CxCA = circumflex coronary artery; DIAG 1 = first diagonal; DIAG 2 = second diagonal; LAD = left anterior descending; LCA = left coronary artery; OAM = obtusum marginalis; PD = posterior descending; RCA = right coronary artery; RM = right marginal.

mally located obstructions should be considered first, but if the aneurysms extend distally, severe distal stenosis is present, or substantial proximal thrombus exists, or a combination of all 3, then serious consideration should be given to cardiac transplantation.

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Transesophageal Echocardiographic Findings of Papillary Muscle Rupture

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Rupture of a papillary muscle is a rare complication of myocardial infarction or trauma.¹ Echocardiographic information is very useful in the diagnosis of ruptured papillary muscle, and for

evaluation of left ventricular function and the degree of mitral regurgitation. A ruptured papillary muscle is not always visualized clearly by transthoracic echocardiography, but may be demonstrated more accurately by transesophageal echocardiography. We studied 2 patients with ruptured papillary muscle, 1 caused by traffic trauma and the other by acute myocardial infarction. The transesophageal echocardiographic

findings of these patients are described.

Patient 1: A 17-year-old high school boy was referred to our hospital because of severe pulmonary congestion on July 19, 1990. He was riding a motorcycle and collided with another motorcycle on July 11, 1990. He was admitted to another hospital. A chest x-ray showed left rib fractures and left hemothorax. On his second day in the hospital, he became critically ill with acute pulmonary edema and was transferred to our hospital under mechanical ventilation. On admission, his blood pressure was

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80/40 mm Hg and his pulse rate was 120 beats/min with regular rhythm. There was a grade 4/6 holosystolic murmur at the apex. Chest x-ray revealed marked pulmonary congestion, and an electrocardiogram showed sinus tachycardia without ST-T-wave abnormality. Pulmonary capillary wedge pressure, obtained at bedside with a Swan-Ganz catheter, was 20 mm Hg (mean) and 58 mm Hg (v wave). Transthoracic echocardiography could not show a

clear cardiac image because of left hemothorax and pneumothorax. Transesophageal echocardiography showed a large mass, 2.0 cm, attached to the anterolateral side of the mitral valve that moved quickly back and forth in the left atrium during systole and in the left ventricle during diastole (Figure 1). Color flow mapping showed severe mitral regurgitation. An emergent mitral valve replacement under the diagnosis of mitral regurgitation due to ruptured papillary muscle was performed. Total rupture of the anterolateral papillary muscle was confirmed by the operative findings (Figure 2). The postoperative course was uneventful, with mild dysfunction of the liver.

Patient 2: A 78-year-old man was admitted to our coronary care unit with acute inferior myocardial

infarction on October 15, 1990. On physical examination, his blood pressure was 100/70 mm Hg and his heart rate was 58 beats/min. There was no heart murmur or rales. An electrocardiogram showed sinus rhythm with ST-segment elevation in leads II, III and aVf and ST-segment depression in leads V₂ to V₅. A coronary angiogram demonstrated total obstruction of the left circumflex artery, and a left ventriculogram showed mild hypokinesia at the inferior wall and no mitral regurgitation. On his eighth day in the hospital, the patient complained of dyspnea, and a new grade 3/6 holosystolic murmur was audible at the apex and was also transmitted to the left axilla. Transthoracic echocardiography revealed a prolapse of the posterior leaflet of the mitral valve and a small mass attached to the posteromedial side of the mitral valve. Color flow mapping showed moderate mitral regurgitation. Transesophageal echocardiography clearly showed the ruptured papillary muscle prolapsing into the left atrium during systole (Figure 3). A chest x-ray demonstrated pulmonary congestion and the pulmonary capillary wedge pressure by Swan-Ganz catheter was 20 mm Hg. Mitral valve replacement was performed 15 days after the rupture of the papillary muscle to prevent sudden deterioration of hemodynamics. Rupture of the posterior papillary muscle was confirmed by the operative findings (Figure 4). The postoperative course of the patient was uneventful.

In our first patient, acute left heart failure developed soon after admission. Rupture of a papillary muscle was accurately diagnosed by transesophageal echocardiography. To our knowledge, this is the first report of traumatic rupture of papillary muscle demonstrated by transesophageal echocardiography.

Ruptured papillary muscle due to myocardial infarction is also a rare



FIGURE 1. Transesophageal echocardiographic 4-chamber view. Ruptured papillary muscle is visible in the left ventricular inflow at the early phase of diastole (top) and in the left ventricular outflow at the late phase of diastole (bottom). This large mass is moving redundantly in the left atrium (LA) during systole and the left ventricle during diastole. LV = left ventricle; MV = mitral valve; RV = right ventricle.

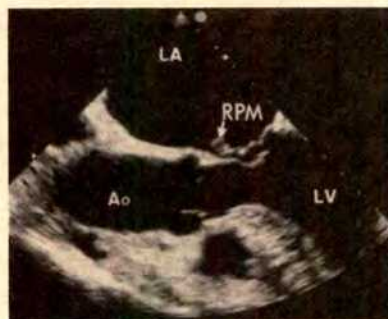


FIGURE 3. Transesophageal echocardiogram shows a ruptured papillary muscle (RPM) (arrow) attached to the posterior leaflet of the mitral valve in the left atrium (LA) during systole. Ao = aorta; LV = left ventricle.



FIGURE 2. Surgical specimen illustrates the completely ruptured trunk of the papillary muscle.

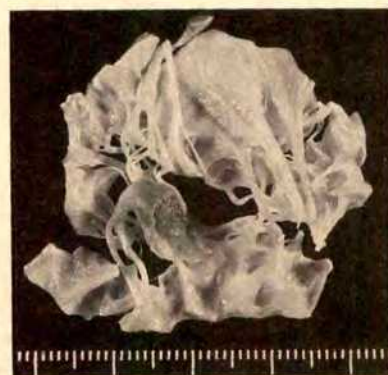


FIGURE 4. Operative specimen demonstrates a ruptured papillary muscle at the posteromedial side of the mitral valve.

complication, but the clinical features and the echocardiographic findings are well documented.²⁻⁴ In some patients with ruptured papillary muscle, it is not always easy to demonstrate the small ruptured tip clearly or to differentiate ruptured chordae tendineae from ruptured papillary muscle by transthoracic echocardiography. In addition, transesophageal echocardiography can show high-resolution images of the structures in the left atrium without any interference from the lungs

or ribs. In our second patient, transesophageal echocardiography gave us clearer information about a ruptured papillary muscle than transthoracic echocardiography did.

Thus, the clear image of a ruptured papillary muscle by transesophageal echocardiography suggests that this technique will play an important role in making accurate decisions for emergent operations.⁵

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Should Antibiotic Prophylaxis Be Recommended for All Patients with Mitral Valve Prolapse?

The recent article by Tofler and Tofler¹ on the use of auscultation to follow patients with mitral valve prolapse (MVP) is extremely important, particularly with respect to the complication of infective endocarditis. The question about the use of antibiotic prophylaxis often arises when a patient with MVP has only a midsystolic click or clicks and no midsystolic or late-systolic murmur.^{2,3} In the longitudinal study reported by Tofler and Tofler during the follow-up period of 8 years (range 1 to 30), not a single instance of infective endocarditis was encountered. This is a striking finding in view of the fact that MVP is nowadays the most common underlying cardiac lesion for infective endocarditis.⁴ Antibiotic prophylaxis was recommended by Tofler and Tofler in all their patients with a midsystolic click or clicks, whether or not there was also a systolic murmur.

One has to be certain that a patient with MVP has no murmur. Because the systolic murmur of mitral regurgitation in MVP may not be constantly present, meticulous auscultation must be performed at each office visit before concluding that there is no murmur.^{5,6} Repeated auscultation in various body positions and the use of various maneuvers, especially Valsalva,^{5,7} are needed.

As Tofler and Tofler pointed out, there is no substitute for careful auscultation. Although the "ready acceptance of the echocardiographic finding of mitral valve prolapse as a clinical diagnosis reflects the homage we pay to technology,"¹ the day-to-day management of the

patient with MVP still depends on the intelligent use of a stethoscope.

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18 December 1990

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Angiographic Progression to Total Coronary Occlusion in Hyperlipidemic Patients After Acute Myocardial Infarction

We read with interest the excellent study by Bissett et al¹ concerning the progression to total coronary artery occlusion. This prospective serial angiographic study showed that the extent of the initial coronary artery narrowing was significantly associated with the risk of progression to total occlusion in hyperlipidemic patients who had previously had an acute myocardial infarction. The results of this study appear to be different from those that we² and Ambrose et al³ recently reported. Both these studies found that the coronary occlusions responsible for acute myocardial infarction frequently occurred in coronary arteries that did not previously have severely stenotic lesions. Thus, the severity of the preexisting coronary disease predicted neither the time nor the location of the occlusion subsequently causing the myocardial infarction. Similarly, Brown et al⁴ found that the stenosis underlying thrombus in patients

with acute myocardial infarction produce a stenosis $\leq 60\%$ in diameter in most patients. How can the different conclusions of these studies be reconciled with the recent report of Bissett et al? There are 2 potential explanations.

First, Bissett studied angiographic progression to total occlusion, not occlusion-producing myocardial infarction. In fact, coronary occlusion produced a myocardial infarction in only 7 of 30 of their patients with occlusions at 3 years, and in 25 of 39 patients at 5 years. It is possible that the progression of severely stenotic lesions to total occlusion did not produce myocardial infarction because of the preexisting stimulus for collateral development. It would be very helpful to know the severity of the preexisting stenosis in the subset of patients in whom total occlusion produced myocardial infarction. Second, the patients in the study reported by Bissett et al¹ had previously had myocardial infarctions. It is possible that many of the very high-grade stenoses present on the first angiogram were actually the culprit lesions that had previously caused a myocardial infarction. These lesions may behave very differently from lesions that have not previously produced a myocardial infarction. In this regard, it would be very helpful to know how many of the high-grade lesions were the culprit lesions responsible for the myocardial infarction occurring before entry into the study.

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Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

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REPLY: Studies by Little,¹ Ambrose² and their co-workers have established that myocardial infarction frequently results from progression of coronary lesions <60%. Conversely, data from the Coronary Artery Surgery Study have suggested a spectrum of risk, with the highest probability of myocardial infarction occurring in lesions >90% and a 3-year infarction rate of only 2% for lesions of the left anterior descending coronary artery with <50% luminal narrowing.³ Based on these data it appears likely that a patient with several lesions of variable severity would be subject to cumulative risk with variation in the natural history of disease, lesion morphology,⁴ and other factors influencing the eventual outcome. The frequency distribution of lesions resulting in complete obstruction would then depend on the method of study, whether grouped by individual patients with a spectrum of lesions (for example, four 25 to 50% lesions and one 70 to 90% lesion), or stratified for lesion severity across patient populations, as in our report. Detection of a difference in the event rate (i.e., progression to total occlusion) from 5 to 15% with 90% certainty and a significance level of 0.05 would require a minimal sample of approximately 185 lesions for each type of risk.

The use of prospective serial angiography identified a number of patients with progression to complete occlusion without clinical evidence of infarction, information that would not have been included in event-guided angiographic studies. The number of patients reported without clinical evidence of myocardial infarction associated with

progression to total occlusion by 5 years should read 24 of 39 patients (62%). The proportion of patients progressing to total occlusion without clinical evidence of infarction was statistically similar at 3 and 5 years ($p = 0.39$). Collateral circulation was noted in 83% of patients at 3 years and in 92% at 5 years.

Inspection of Table IV of our paper reveals a general correspondence between the degree of stenosis and the incidence of subsequent progression to total occlusion in this postinfarction population. Although lesions with minimal stenosis infrequently progressed to complete occlusion, the cumulative risk could present a significant hazard in patients with multivessel disease.

Joe K. Bissett, MD
Richard P. Wyeth, MA
Little Rock, Arkansas
15 January 1991

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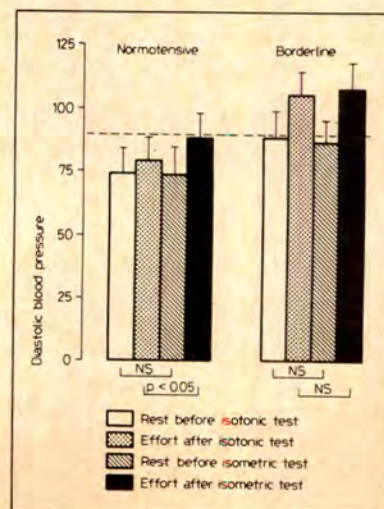
Use of Isometric Exercise Testing Can Replace Isotonic Testing to Detect and Evaluate Hypertensive Populations

We read with interest the article by Wilson et al¹ indicating an exaggerated pressure response to exer-

cise testing in men at risk of systemic hypertension. Exercise testing provides a means of detecting individual risk that may not be detected by blood pressure measured routinely at rest.^{2,3} Although it has been well established that dynamic (isotonic) exercise testing distinguishes among normotensive persons, those with borderline hypertension and those at high risk of developing systemic hypertension, it is limited by the time needed to perform it, expensive equipment, the need for highly trained personnel, and its inconvenience for large-scale screening.

We previously observed a good correlation between the isotonic dynamic stress test and the hand-grip static (isometric) test (Figure 1) (sensitivity, 98%, specificity, 78%, predictive value of an abnormal test, 90%) in a study that compared diastolic blood pressure after isotonic testing (treadmill exercise stress test) with static (isometric hand-grip) testing using a modified protocol developed in our unit.⁴ We observed that 90 seconds of gripping at 30% of maximal voluntary isometric contraction elevated blood pressure levels only in latent, borderline and hypertensive subjects, whereas normotensive subjects responded normally.⁴ We⁵ and others⁶ used hand-gripping as a simple and accessible method for monitoring antihypertensive therapy.

We suggest that hand-gripping could be introduced to replace more expensive and cumbersome dynam-



ic testing for the screening, detection and evaluation of hypertension, in a strategy designed to evaluate hypertensior during effort, as suggested by Wilson et al.¹

**Angel Cantor
Noah Liel**

Beer Sheva, Israel
22 January 1991

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Lipid Profiles After Cardiac Transplantation

In their article, Rudas et al¹ reported to have estimated low-density lipoprotein (LDL) cholesterol with the Friedewald formula,² in which the very low-density lipoprotein cholesterol is approximated as serum triglycerides divided by 5. Unfortunately, this equation can be applied without correction only if the results are expressed in mg/dl. When Systeme International (S.I.) units are used, the equation must be adapted because the conversion factors for triglycerides and for cholesterol are different. With S.I. units, the Friedewald formula becomes: LDL cholesterol = total cholesterol - [serum triglycerides / 2.18 + high-density lipoprotein

cholesterol]. As can be seen from the corrected equation, the LDL cholesterol would be overestimated with the original formula when S.I. units are used. Fortunately, the authors seem to have used the corrected formula, as can be deduced from the results provided.

This mistake is common in the literature in North America,³⁻⁶ reflecting the lack of familiarity with S.I. units, since conventional units are still widely used. Authors and reviewers of articles should try not to add to the existing confusion. A simple test to check if an equation can be used with both types of units is to first make the calculation with conventional units and then convert all results in S.I. units before redoing the calculation. If the final results differ, the equation needs to be adapted before using it with S.I. units.

Jacques Massé, MD

Quebec City, Canada
26 November 1990

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Radionuclide Exercise Response in Young Asymptomatic Chronic Alcoholics

The article by Cerquiera et al¹ uses both rest echocardiography and resting and exercise radionuclide ventriculography to test for the presence of preclinical alcoholic cardiomyopathy in 25 asymptomatic

chronic alcoholics aged <40 years. The results of this study revealed normal resting echocardiographic measurements and normal resting and exercise radionuclide response for the alcoholics as a group (only 3 alcoholics failed to show a normal increase in ejection fraction), leading the authors to conclude that preclinical cardiac dysfunction is rare in this patient group.¹ Unmentioned, however, was a previous publication by our group, which studied a similar patient population by essentially the same techniques.² New findings by Cerquiera et al¹ include the assessment of diastolic function by radionuclide testing, as well as unaltered red blood cell levels of selenium and thiamine among alcoholics. In addition to showing normal resting and exercise ejection fractions early and later after study patients discontinued alcohol, our data showed a decreased heart rate-blood pressure product (compared with that found early after withdrawal from alcohol) at each work load during follow-up exercise (2 to 4 weeks later) consistent with an increased myocardial oxygen demand very early after ending alcohol abuse.² Our data showed that 1 of 12 had a minimally acceptable increase in ejection fraction with exercise (increase by only 5 units). Thus, the study of Cerquiera et al¹ and our study² both give similar, as well as complementary, results.

Ralph Moskowitz, MD

Martinez, California
25 February 1991

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Cause of Ventricular Arrhythmia

Regarding your solicitation to a wager in the December 1, 1990 *Journal*,¹ I'm afraid that I'm going to have to take that bet. You argue

that elevated lipids are associated with atherogenesis. The ischemia that results from atherosclerotic occlusion causes the myocardial electrical instability that results in the arrhythmias of sudden cardiac death (SCD). If only we could reduce lipid levels by diet or drugs, then that chain would be broken. Since we're all dietary weaklings, "lipid-lowering agents eventually will prove to be the best antiarrhythmic agents."

I agree that a more temperate intake of fat by our population would probably reduce the incidence of SCD in exactly the manner you suggest, but "best" is a mighty big word.

I suggest to you that a better intervention would be something that separates atherogenesis from elevated lipids, something that prevents the formation of atherosclerotic plaques regardless of diet and regardless of lipid levels. I would further suggest that if that something could also be shown to directly stabilize the electrical flux in the myocardium, that would be "the best antiarrhythmic agent." And, if that something had a very low side-effect profile (as opposed to lipid-lowering agents), that would be a cherry on top.

There are several somethings like that on the shelf right now. They include all of the calcium channel blockers,² the angiotensin-converting enzyme inhibitors,³ the mineral magnesium,⁴ and dietary omega-3 fatty acids.⁵ It appears that just about anything that reduces the velocity/volume of calcium flowing into the myocardial cell is "the best antiarrhythmic agent." They all separate atherogenesis from elevated lipids.

Take a look at your argument once more. Elevated lipids are definitely atherogenic, but how? What, exactly, does cholesterol do? Among other things, cholesterol⁶ and low-density lipoprotein⁷ directly raise the level of intracellular calcium (Ca_i) in vascular smooth muscle cells. Interventions that prevent that rise in Ca_i separate elevated lipids from atherogenesis.²⁻⁴

Atherosclerotic occlusions cause ischemia, but what is it about ischemia that is arrhythmogenic? Oxy-

gen deprivation causes a dramatic rise in Ca_i (which may be worsened by reperfusion)⁸ in the cells of the heart. That lowers the threshold of the action potential in those cells and makes the heart vulnerable to aberrant beats, reentrance and circus movement. Interventions that specifically prevent that rise in Ca_i separate ischemia from arrhythmogenesis.⁹

Breaking this physiologic chain at the level of dietary fat is possible but not, as we all know, very easy to implement. Lipid-lowering drugs may, in the long run, produce the desired effect, but it is via an indirect route with many side effects. It is the elevation in Ca_i that appears to be the key. And, as such, a direct attack on that would be the simplest and "best" approach to reducing SCD.

Abnormally elevated levels of Ca_i are found in patients with heart failure,¹⁰ ischemic heart disease,¹¹ hypertension,¹² diabetes,¹³ and in the obese¹⁴—the very people most at risk of SCD. Our "best bet" for reducing SCD, better than lipid control, may well be the prevention of treatment of this abnormal Ca_i elevation, which seems to be directly responsible for a significant part of the pathogenesis of SCD.

James A. Landauer
Denver, Colorado
17 December 1990

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Mitral Regurgitation Improves When Aortic Valve Area Increases Significantly

We read with interest the report by Adams and Otto¹ that noted a lack of improvement in coexisting mitral regurgitation (MR) after relief of valvular aortic stenosis, contradicting previous reports.^{2,3} We have encountered this preoperative clinical dilemma frequently. Be-

cause replacement of both the aortic and mitral valves increases operative complexity, morbidity and mortality, we have generally recommended aortic valve replacement without mitral replacement or repair unless moderate to severe MR was present.

The investigators state that "it is clear that the lack of improvement in MR was not related to incomplete relief of aortic stenosis because there was no difference between the subgroups with valve replacement or valvuloplasty." We would disagree. In reviewing the data from Table I in the report, we noted several patients with little or no improvement in their aortic valve area after valve replacement or valvuloplasty. To assess whether MR decreased in patients with a significant reduction in afterload assessed by an improvement in aortic valve area, we reanalyzed the data.

Criteria of success after aortic valve replacement or valvuloplasty are variable. The valvuloplasty registry has used aortic valve area improvement of $\geq 25\%$ and a post-procedure aortic valve area $\geq 0.8 \text{ cm}^2$ as criteria of success.⁴ If groups are divided based on these criteria, then 64% of patients considered unsuccessful had MR that did not improve and 32% of successful patients had MR that decreased ($p < 0.01$). If more rigid criteria for success are used (aortic valve area $\geq 0.8 \text{ cm}^2$ and 50% increase in aortic valve area), then the results are more striking. MR did not improve in 88% of unsuccessful aortic procedures and MR improved in 73% of those in whom it was successful.

We therefore might conclude from these data that patients with significant improvement in aortic valve area and a significant reduc-

tion in afterload after intervention will often have an improvement in MR severity, whereas patients without such improvement will not.

This reanalysis is important because, in the data reported, many patients did not have a significant improvement in their aortic valve area. Based on the report's conclusion, practicing physicians may alter their traditional strategy of aortic valve replacement alone for patients with aortic stenosis and MR. This would be a mistake. Based on previous reports and on reanalysis of the data of Adams and Otto, there is convincing evidence that MR is improved when there is significant relief of valvular aortic stenosis.

Seth D. Bilazarian, MD
Ravin Davidoff, MD

Boston, Massachusetts
22 March 1991

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REPLY: Bilazarian and Davidoff raise the question of whether the severity of coexisting MR improves in patients meeting strict criteria for successful relief of aortic steno-

sis. Note that 22 of 24 patients (92%) of the valve replacement group meet one of these criteria—the exceptions were a patient with a small Duromedics valve and a patient with only moderate stenosis before valve replacement—yet we found no significant change in regurgitant severity in this group.

Using the criteria of success indicated in the letter from Bilazarian and Davidoff, and using our data (Table I), we are unable to reproduce their reported percentages of success. We find that only 40% (12 of 30 patients) improved using definition 1 and 52% (11 of 21) improved using definition 2. In addition, the method used to derive p values is unclear in their letter. The appropriate statistic is the nonparametric sign test, which includes patients who had apparent worsening of mitral regurgitant severity after the procedure, as well as those with apparent improvement. Finally, it should be noted that in patients who did show improvement after successful relief of aortic stenosis, the degree of improvement was clinically insignificant (i.e., from 1+ to 0) in the vast majority.

Our data certainly are not definitive and a larger, prospective study (including more patients with moderate and severe mitral regurgitation) on the influence of relief of aortic stenosis on coexisting mitral regurgitation is needed. However, our data do suggest that a clinically significant decrease in mitral regurgitant severity is not always seen after relief of aortic stenosis, so that the decision whether to perform concurrent mitral valve surgery must be carefully considered in each individual patient.

Catherine M. Otto, MD
Seattle, Washington

Peter B. Adams, MD
Rochester, Minnesota

1 May 1991

The American Journal of Cardiology[®]

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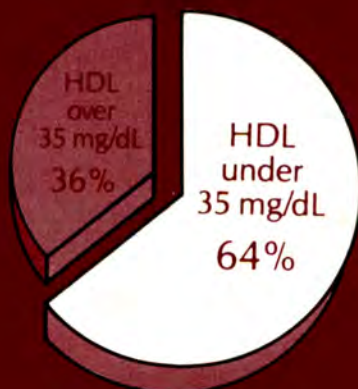
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CORONARY ARTERY DISEASE

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CORONARY ARTERY DISEASE

569**Comparison of Chest Pain, Electrocardiographic Changes and Thallium-201 Scintigraphy During Varying Exercise Intensities in Men with Stable Angina Pectoris**

Gary V. Heller, Imtiaz Ahmed, Peter L. Tilkemeier, Marilyn M. Barbour, and Carol Ewing Garber

The present study was performed to test the concept of the ischemic cascade by evaluating the presence of anginal symptoms, electrocardiographic changes and reversible thallium-201 defects resulting from 2 different levels of exercise (symptom-limited and submaximal) in 19 patients with exercise-induced ischemia. Incremental exercise resulted in anginal symptoms in 84% of patients, and electrocardiographic changes and reversible thallium-201 defects in all patients. In contrast, submaximal exercise produced anginal symptoms in only 26% ($p < 0.01$), electrocardiographic changes in only 47% ($p < 0.05$), but resulted in thallium-201 defects in 89% of the patients ($p =$ not significant). These findings confirm the sequence of the ischemic cascade using 2 levels of exercise and demonstrate that the cascade theory is applicable during varying ischemic intensities in the same patient.

575**Usefulness of Technetium-99m-MIBI and Thallium-201 in Tomographic Imaging Combined with High-Dose Dipyridamole and Handgrip Exercise for Detecting Coronary Artery Disease**

Raimo Kettunen, Heikki V. Huikuri, Juhani Heikkilä, and Juha T. Takkunen

Forty-two patients with stable angina pectoris referred for quantitative coronary angiography were examined by Tc-99m-hexakis-2-methoxy-2-methylpropyl-isonitrile (MIBI) tomography combined with high-dose dipyridamole infusion (0.7 mg/kg) and handgrip exercise. Twenty-seven of 33 (82%) stenotic lesions of the left anterior descending artery, 17 of 28 (61%) from the left circumflex artery, and 28 of 31 (90%) from the right coronary artery were correctly identified. In a subset of 21 patients also referred for thallium-201 scintigraphy, the overall diseased vessel identification rate was 76%, compared with 83% obtained with Tc-99m-MIBI ($p =$ not significant). The rate of noncardiac adverse effects related to high-dose dipyridamole remained rather low (5%).

Continued on page A18



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Efficacy of Slow-Release Nifedipine on Myocardial Ischemic Episodes in Variant Angina Pectoris

Yasuhiro Morikami and Hirofumi Yasue

To evaluate the efficacy of slow-release nifedipine on ischemic episodes in patients with variant angina, a single-blind crossover study with ambulatory electrocardiographic monitoring was performed in 15 patients. In all there were 646 ischemic episodes during the study period, and 618 of them occurred during placebo periods. Sixty-nine percent of the episodes in placebo periods were asymptomatic. The number of anginal attacks, nitroglycerin tablets taken, ST-segment elevation and total ischemic duration significantly decreased during nifedipine periods compared with the number during the placebo period, respectively ($p < 0.01$ or 0.05). Twenty-eight ischemic episodes occurred during the nifedipine periods, and they occurred when the plasma level of nifedipine was low. The administration of slow-release nifedipine is highly effective in suppressing not only symptomatic but also asymptomatic myocardial ischemia in patients with variant angina. The timing of the administration of slow-release nifedipine is one of the important factors in suppressing ischemic episodes.

585

Comparison of Intravenous Urokinase Plus Heparin Versus Heparin Alone in Acute Myocardial Infarction

Paolo Rossi and Leonardo Bolognese

In a randomized trial of the effects of intravenous urokinase plus heparin versus heparin alone, 2,531 patients with acute myocardial infarction were randomized to receive either intravenous urokinase (1 million U bolus repeated after 60 minutes) plus heparin (10,000 U bolus, followed by 1,000 U/hour for 48 hours) or heparin alone (infused at the same rate). Complete data were obtained in 2,201 patients. At 16 days, overall hospital mortality was 7.9% in the urokinase and 8.3% in the heparin group (p = not significant). Among patients with anterior infarction, mortality was 10.3% in the urokinase and 13.9% in the heparin group (p = 0.09; relative risk = 0.71). The incidence of major bleeding (urokinase group 0.44%, heparin group 0.37%), as well as the overall incidence of stroke (urokinase group 0.35%, heparin group 0.20%) was similar in the 2 groups. In conclusion, both drug regimens achieve comparable mortality rates with a similar incidence of bleeding complications. The combination of urokinase and heparin produces a 25% reduction in risk in patients with anterior infarction.

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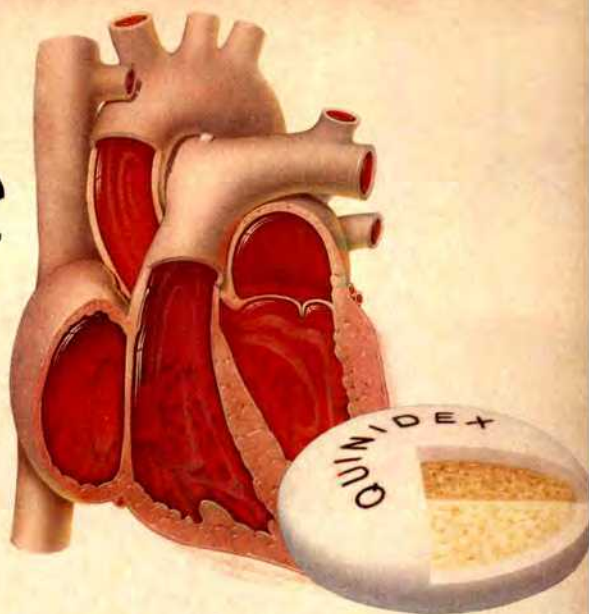
Prediction of Major Cardiac Events After Peripheral Vascular Surgery Using Dipyridamole Echocardiography

Marc D. Tischler, Thomas H. Lee, Alan T. Hirsch, Christopher P. Lord, Lee Goldman, Mark A. Creager, and Richard T. Lee

One hundred nine patients were prospectively studied before peripheral vascular surgery to determine the positive predictive value of dipyridamole echocardiography for major cardiac events. Nine patients had positive dipyridamole echocardiograms as defined by the development of new

Continued on page A20

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The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: General—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients:—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests:—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug
Quinidine with anticholinergic drugs
Quinidine with cholinergic drugs
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics
Quinidine with coumarin anticoagulants
Quinidine with tubocurarine, succinylcholine and desamethopium
Quinidine with phenothiazines and reserpine
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)
Quinidine with digoxin
Quinidine with amiodarone
Quinidine with cimetidine
Quinidine with ranitidine
Quinidine with verapamil
Quinidine with nifedipine

Effect

Additive vagolytic effect
Antagonism of cholinergic effects
Alkalinization of urine resulting in decreased excretion of quinidine
Reduction of clotting factor concentrations
Potentialization of neuromuscular blockade
Additive cardiac depressive effects
Decreased plasma half-life of quinidine
Increased serum concentration of digoxin (See Warnings)
Increased serum concentration of quinidine
Prolonged quinidine half-life and an increase in serum quinidine level
Premature ventricular contractions and/or bigeminy
Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinidine, quinidine has been reported to have cytotoxic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery:—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have cytotoxic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers:—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Phlebotic Use:—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal:—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular:—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System:—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otic:—Disturbed hearing (tinnitus, decreased auditory acuity); disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata); optic neuritis; reduced visual field.

Dermatologic:—Cutaneous flushing with intense pruritus; photosensitivity; urticaria; rash; icterus; exfoliative eruptions; psoriasis; abnormalities of pigmentation.

Hypersensitivity:—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), periora, vasculitis.

Hematologic:—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic:—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous:—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Twice-a-day dosing* to make life easier for your arrhythmia patients. That's the Quinidex® advantage. Because, like the heart, Quinidex Extentabs® have been uniquely constructed for dependable around-the-clock performance.

*Some patients may require t.i.d. dosing.



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regional wall motion abnormalities. Of these, 7 had major cardiac events. Of the 100 patients having negative studies, 1 patient had a major cardiac event. Thus, the positive and negative predictive values were 78 and 99%, respectively. The relative risk of having a major cardiac event after elective vascular surgery was 78 (95% confidence interval, 11 to 564; $p < 0.0001$) in patients with abnormal dipyridamole echocardiograms. If these results are extended and confirmed by other investigators, dipyridamole echocardiography may be a useful test for assessing cardiac risk in patients undergoing peripheral vascular surgery.

598**Impairment of Left Ventricular Function During Coronary Angioplastic Occlusion Evaluated with a Nonimaging Scintillation Probe**

Andreas Hartmann, Frank-Dieter Maul, Michael Zimny, Harald Klepzig, Christian Vallbracht, Hans-Georg Kneissl, Rainer Schröder, Gustav Hör, and Martin Kaltenbach

Left ventricular function was evaluated with a newly developed miniaturized cesium iodide scintillation detector before, during and after coronary occlusion during coronary angioplasty in 18 patients (age 59 ± 10 years) with coronary artery stenosis $>70\%$. Systolic and diastolic left ventricular function as determined by changes in ejection fraction, peak ejection rate, peak filling rate, and end-systolic and end-diastolic volumes were impaired during coronary occlusion. Sequential dilatations did not further decrease left ventricular function if a sufficient interval was kept.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES**603****Use of Amiodarone for Short-Term and Adjuvant Therapy in Young Patients**

Giacomo Pongiglione, Janette F. Strasburger, Barbara J. Deal, and D. Woodrow Benson, Jr.

Amiodarone was considered effective as a sole antiarrhythmic agent in 21 of 47 (45%) patients for an average treatment duration of 12 months. Treatment was ineffective but was continued in 11 (23%) patients; in 10 of these patients amiodarone was adjuvant to other antiarrhythmic drugs. Thus, amiodarone was clinically useful in 32 (68%) patients; amiodarone was considered ineffective and was withdrawn in 15 (32%) patients. No patient required cardiac pacemaker implant during therapy. Torsades de pointes and cardiac arrest occurred in 1 patient each after 9 and 14 days of therapy, respectively. Two patients underwent successful cardiac transplant after 2 and 14 months of amiodarone administration, respectively. Amiodarone was administered as short-term treatment (<18 months) in 7 infants (age <18 months), and after cessation of treatment, there was no tachycardia recurrence for 4 to 24 months. In pediatric patients, amiodarone is useful both as short-term treatment and as adjuvant therapy with other antiarrhythmic drugs.

Continued on page A25

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Effects of Enflurane on Inducibility of Ventricular Tachycardia

Christine Hief, Martin Borggreffe, Xu Chen, Antonio Martinez-Rubio, Thomas Hachenberg, Peter Lawin, and Günter Breithardt

The effects of enflurane on cardiac electrophysiologic parameters and on inducibility of ventricular tachycardia (VT) by programmed stimulation were studied in 12 patients (11 men and 1 woman, mean age \pm standard deviation 55 ± 8 years) with drug refractory sustained monomorphic VT who underwent transcatheter ablation with high-energy direct-current shocks. Programmed ventricular stimulation was performed on 2 separate days (mean interval 19 days). Two baseline studies were performed several days before and at the beginning of the ablation procedure while the patients were awake and nonsedated. The third study was performed 15 to 30 minutes after administration of anesthesia (enflurane, oxygen and nitrous oxide). QTc interval increased significantly (456 ± 51 to 482 ± 57 ms, $p < 0.05$), whereas rate of sinus rhythm, QRS duration, PQ interval and ventricular effective refractory period were unaltered after initiation of anesthesia. Clinical VT was inducible in all patients. However, in 1 patient, induction of VT was only possible by pacing in the left ventricle after enflurane administration.

614

Dispersion of Ventricular Repolarization in the Long QT Syndrome

Luigi De Ambroggi, Maria S. Negroni, Emanuela Monza, Tito Bertoni, and Peter J. Schwartz

In 40 patients with idiopathic long QT syndrome and in 30 healthy control subjects, body surface potential maps (117 chest leads) were recorded in order to identify markers of electrical disparities of the ventricular repolarization. Maps of the integral values of QRST were calculated: a multipolar distribution of the values, a marker of gross repolarization inequalities, was found only in 4 patients. To detect minor regional disparities of ventricular recovery, all ST-T waveforms were analyzed in each subject. By applying principal component analysis, a "similarity index" was computed: a low value of the similarity index indicates a large variety of ST-T waves, likely to reflect the disparity of ventricular repolarization. The mean value of similarity index was significantly lower in patients with long QT syndrome than in control subjects (49 ± 10 vs $77 \pm 8\%$); a value $< 61\%$ (2 standard deviations below the mean for controls) was found in 35 of 40 patients and in only 1 control subject (sensitivity 87%, specificity 96%). The low value of the similarity index observed in patients with long QT syndrome suggests a high degree of dispersion of ventricular recovery times, a condition of vulnerability to malignant ventricular arrhythmias.

621

Dimensions of the Human Posterior Septal Space and Coronary Sinus

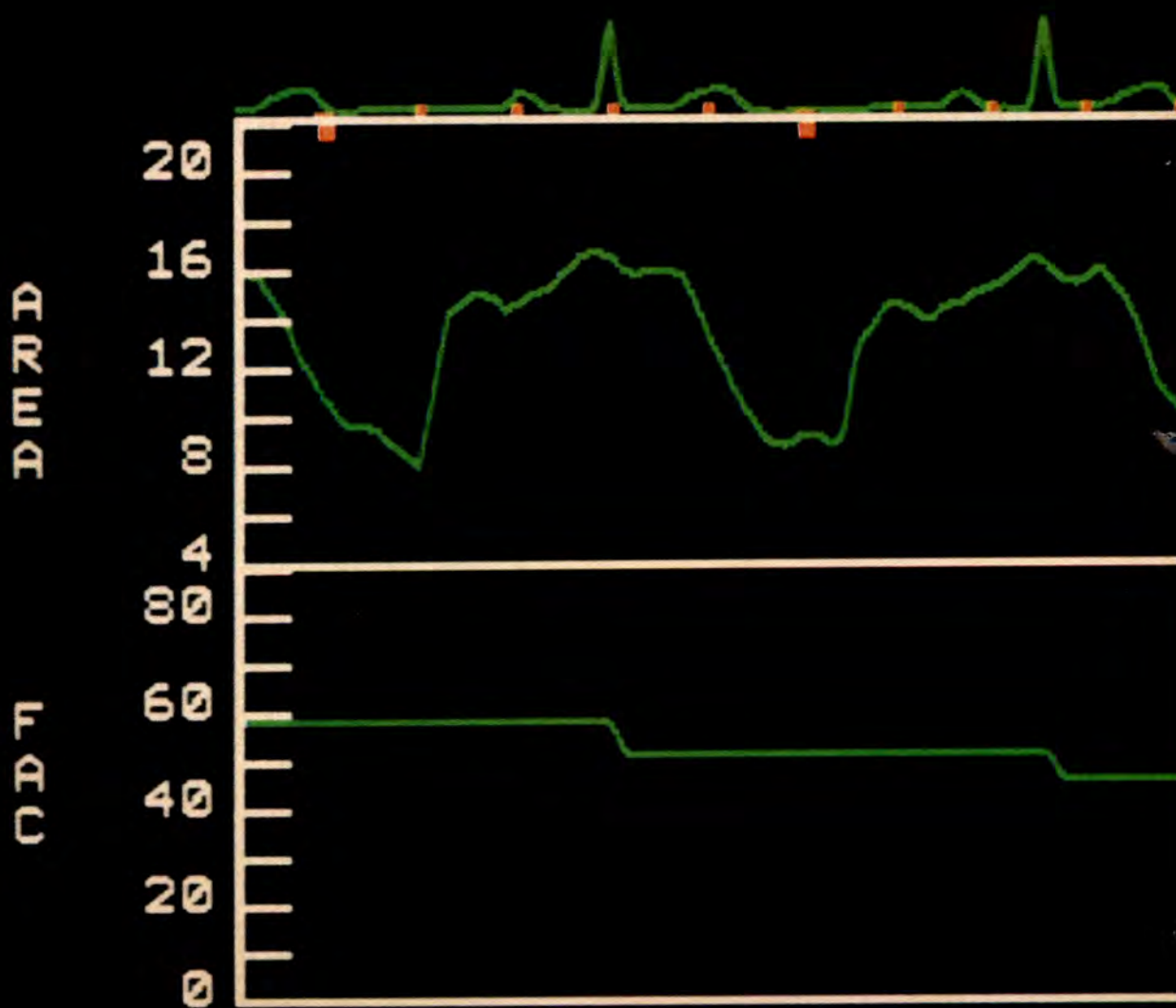
Lloyd M. Davis, Karen Byth, Peter Ellis, Mark A. McGuire, John B. Uther, David A. B. Richards, and David L. Ross

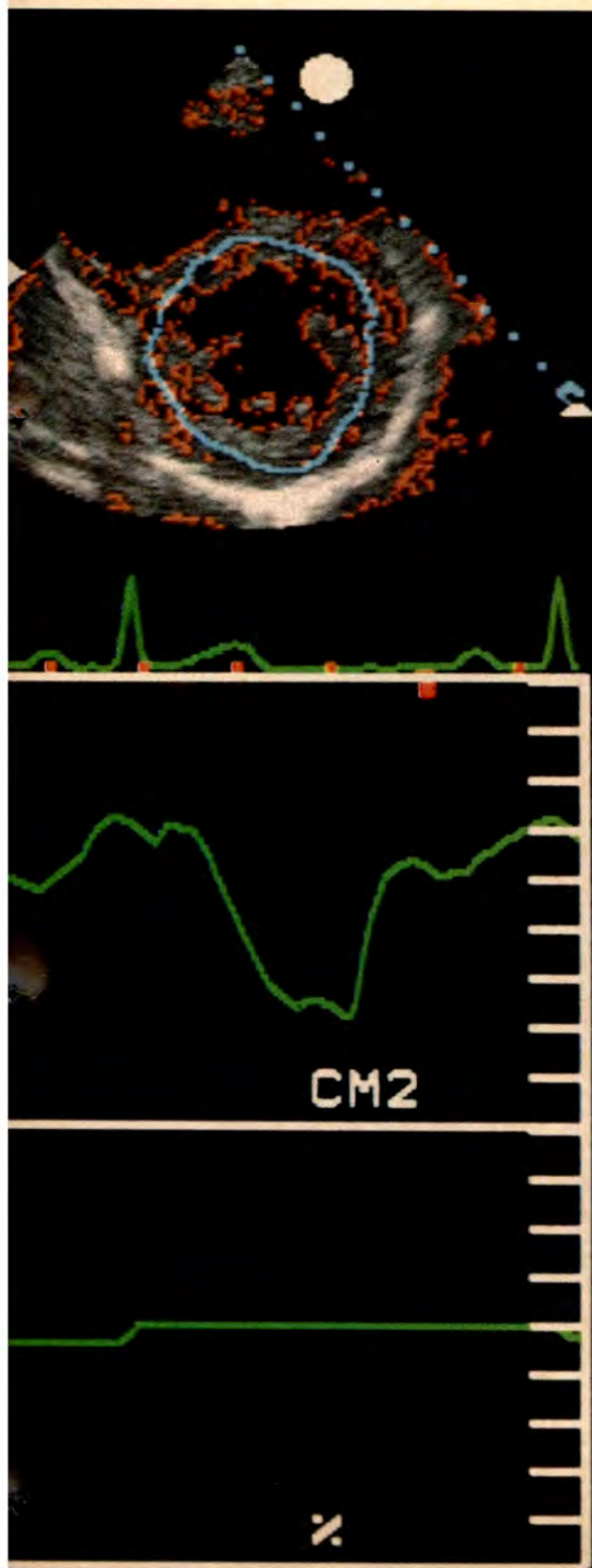
To permit accurate anatomic localization of accessory pathways at electrophysiologic study, the dimensions of the posterior septal space and the

Continued on page A28

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It is a machine that will enable you to make diagnoses with greater confidence. And it will change forever the way you do your job.

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left free wall in 48 adult human cadaver hearts were determined. The results showed that accessory pathways located in the proximal 1.5 cm of the coronary sinus are almost always in the posterior septum, those between 1.5 and 3 cm from the coronary sinus orifice may be in either the left free wall or the posterior septum, and those >3 cm from the coronary sinus orifice are almost invariably in the left free wall. Prediction of the width of the posterior septum in the individual patient was improved by accounting for the combination of patient age and body weight.

626**Stability Over Time of Variables Measuring Heart Period Variability in Normal Subjects**

Robert E. Kleiger, J. Thomas Bigger, Matthew S. Bosner, Mina K. Chung, James R. Cook, Linda M. Rolnitzky, Richard Steinman, and Joseph L. Fleiss

We measured time and frequency domain measures of heart period variability on 14 subjects aged 25 to 55 years (mean \pm standard deviation 32 ± 7) free of cardiac disease. Baseline and placebo 24-hour ambulatory electrocardiograms were performed 3 to 65 days apart. Over this period of time the variables measured showed marked stability. The mean and standard deviations of the measured variables were virtually identical on baseline and placebo recordings, demonstrating a lack of placebo effect. The intraclass correlation coefficients, a measure of intrasubject variability, exceeded 0.8 for most variables, establishing that change in the variables for a single subject is limited. Correlations between certain time and frequency domain measures were very high, establishing their essential equivalence.

CONGESTIVE HEART FAILURE**631****Effectiveness of Imazodan for Treatment of Chronic Congestive Heart Failure**

A. David Goldberg, John Nicklas, and Sidney Goldstein, for the Imazodan Research Group

The efficacy and safety of a new phosphodiesterase inhibitor, imazodan, was investigated in a 12-week multicenter, double-blind, randomized, placebo-controlled trial. The 147 patients with heart failure continued to take their usual therapy including diuretics, digoxin and captopril. Exercise tests were performed monthly. Exercise time increased significantly from baseline in all groups. There was no difference between the groups in changes in ejection fraction, ventricular arrhythmias or in exercise time. There was no significant difference by intent-to-treat analysis in mortality in the imazodan-treated groups compared with those given placebo.

Continued on page A34

ACTIVASE®

ALTEPLASE, RECOMBINANT

A TISSUE PLASMINOGEN ACTIVATOR

Brief Summary

Consult full prescribing information before using.

INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

ACTIVASE® is also indicated in the management of acute massive pulmonary embolism (PE) in adults: for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs, and for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures. The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE®, it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) trauma • Hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

Pulmonary Embolism It should be recognized that the treatment of pulmonary embolism with ACTIVASE®, Alteplase, has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reemboilization due to the lysis of underlying deep venous thrombi should be considered.

PRECAUTIONS: General Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE® if anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites. **Pregnancy (Category C)** Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE®, Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-14 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials¹⁻⁷ is not significantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites. **Allergic Reactions** No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: ACTIVASE® is for intravenous administration only. **ACUTE MYOCARDIAL INFARCTION: Administer ACTIVASE® as soon as possible after the onset of symptoms.**

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.⁸

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

PULMONARY EMBOLISM: The recommended dose is 100 mg administered by intravenous infusion over two hours. Heparin therapy should be instituted or reinstituted near the end of or immediately following the ACTIVASE® infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® may be administered as reconstituted at 1.0 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass bottles are acceptable. ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

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VALVULAR HEART DISEASE

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Comparison of Allografts and Prosthetic Valves when Used for Emergency Aortic Valve Replacement for Active Infective Endocarditis

Flavian M. Lupinetti and John H. Lemmer, Jr.

It is uncertain whether the increased technical demands of allograft aortic valve replacement (AVR) is justified in emergency operations. This study reports 15 patients with acute bacterial or fungal endocarditis who underwent emergency AVR because of severe congestive failure, overwhelming sepsis or cerebral emboli. Eight patients received prosthetic valves (group I) and 7 received human allografts (group II). The groups were comparable in age (group I, 55 years; group II, 51 years), intravenous drug abuse (group I, 1; group II, 3) and previous AVR (group I, 3; group II, 2). Operative deaths occurred in 4 of 8 group I and 1 of 7 group II patients. All surviving patients have been successfully followed (group I, 28 months; group II, 18 months). One group II patient required late reoperation and another group II patient died 10 months postoperatively of noncardiac causes. There were no other late complications or deaths. Allograft AVR can be performed safely in this high-risk patient population.

CARDIOMYOPATHY

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Electrocardiographic Correlates with Left Ventricular Morphology in Idiopathic Dilated Cardiomyopathy

Francesco Pelliccia, Giuseppe Critelli, Cinzia Cianfrocca, Antonio Nigri, and Attilio Reale

To verify whether the electrocardiographic pattern of patients with idiopathic dilated cardiomyopathy (IDC) may be useful in predicting left ventricular (LV) morphology, 12 electrocardiographic criteria for LV enlargement were evaluated in 67 patients with IDC, and were correlated to angiographic and echocardiographic measurements of LV wall thickness, volume and mass. Multiple logistic regression analysis showed that total 12-lead QRS amplitude, voltage criteria of Sokolow and Lyon, overshoot and U-wave inversion were the variables significantly related to LV wall thickness. The sum of T/R wave ratios, the RV_6/RV_5 ratio and the Romhilt-Estes score were predictors of LV end-diastolic volume. Total 12-lead QRS amplitude and the sum of T/R-wave ratios were the only independent predictors of LV mass. Thus, multiple electrocardiographic criteria should be used to better predict LV mass and distinguish reliably between LV wall thickening and dilatation.

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CONGENITAL HEART DISEASE

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Long-Term Assessment of Right Ventricular Diastolic Filling in Patients with Pulmonic Valve Stenosis Successfully Treated in Childhood

Roger P. Vermilion, A. Rebecca Snider, A. Resai Bengur, and Jon N. Meliones

To determine if right ventricular (RV) diastolic filling abnormalities persist long term after successful therapy of pulmonic stenosis (PS), 19 patients were examined with Doppler echocardiography 8 ± 3 years after PS therapy. Tricuspid inflow Doppler diastolic function indexes of the PS follow-up patients were compared with those of 12 age-related control subjects and 14 untreated PS patients. PS follow-up patients had higher peak E velocity, lower peak A velocity, higher 0.33 area fraction, lower A area fraction, and higher E/A velocity and area ratios than untreated PS patients ($p < 0.03$). All Doppler indexes of the PS follow-up patients were the same as those of the control subjects except for the peak E and peak A velocities that were slightly higher and the E/A area ratio that was slightly lower ($p < 0.03$). Thus, at long-term follow-up, all RV diastolic filling indexes of successfully treated PS patients improved compared with untreated PS patients and approached values found in normal subjects. These data suggest that RV diastolic filling abnormalities in PS patients are reversible over the long term and are, thus, probably related to hypertrophy rather than fibrosis and scarring.

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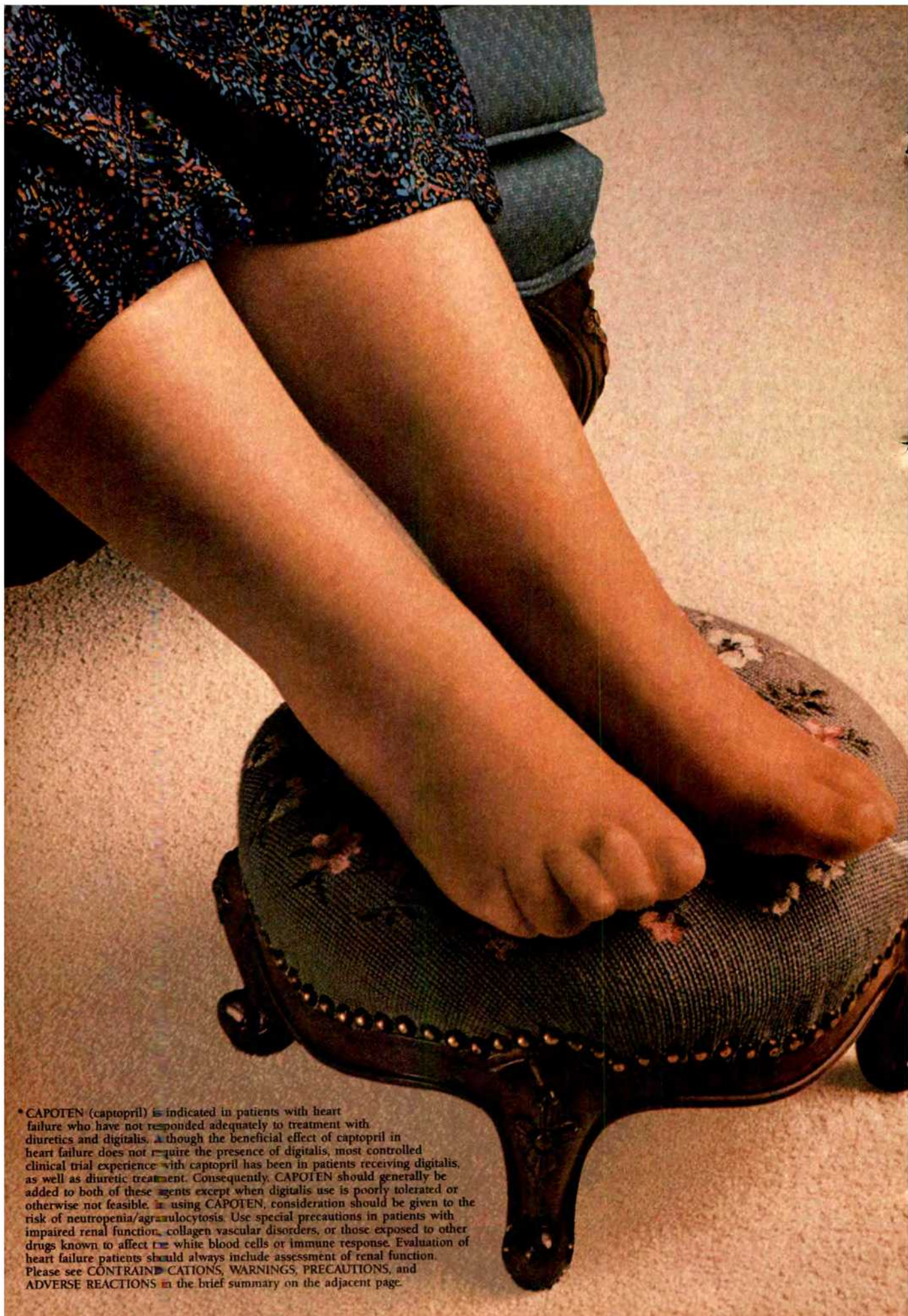
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Factors Influencing Doppler Indexes of Left Ventricular Filling in Healthy Persons

Seppo Voutilainen, Markku Kupari, Mikko Hippeläinen, Kari Karppinen, Markku Ventilä, and Juhani Heikkilä

Ninety-three healthy persons aged 11 to 91 years were studied to assess the factors influencing the Doppler indexes of left ventricular (LV) diastolic function. With advancing age—and with increases in either body mass index, heart rate, diastolic blood pressure or LV mass—the indexes of early filling decreased, whereas with regular modest use of alcohol or regular aerobic exercise they increased ($p < 0.05$ for all). In subjects aged 40 to 60 years, gender was the most important explanatory factor and accounted for 32 to 57% of the variation in the peak atrial velocity, early to atrial peak velocity ratio and atrial filling fraction. Thus, many constitutional and physiologic factors and even life-style can influence Doppler indexes of LV filling. This must be taken into account in the interpretation of individual data in clinical practice.

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* CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to treatment with diuretics and digitalis. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment. Consequently, CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white blood cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

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Bivariate Genetic Analysis of Left Ventricular Mass and Weight in Pubertal Twins (The Medical College of Virginia Twin Study)

Henri A. Verhaaren, Richard M. Schieken, Michael Mosteller, John K. Hewitt, Lindon J. Eaves, and Walter E. Nance

Preventive health decisions require understanding the genetic regulation of left ventricular (LV) mass. We hypothesized that genes common to both could explain the relation between weight and LV mass in children. In early pubertal twins, we asked: (1) How much of the total variance of LV mass is genetic? (2) After accounting for weight and sexual maturity, how much of the remaining variance is genetic? (3) Of the total genetic variance, what proportion is specific for LV mass and what proportion is common to both weight and LV mass? (4) How much of the correlation is explained by genes common to both LV mass and weight? Bivariate genetic analyses confirmed that >90% of the correlation of LV mass and weight is due to common genes. In normotensive children, preventive strategies of weight reduction may have a limited effect on LV mass.

METHODS

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Left Ventricular Ejection Fraction Measured with Doppler Color Flow Mapping Techniques

A. Resai Bengur, A. Rebecca Snider, Roger P. Vermilion, and John C. Freeland

A new technique for measuring left ventricular (LV) ejection fraction (EF) from Doppler color flow mapping was tested in 11 patients (age 0.4 to 22 years). Within 24 hours of cardiac catheterization, 2-dimensional echocardiographic and color Doppler images were obtained from the apical 4-chamber and long-axis views. For the color Doppler images, the color sector was placed so as to include the entire left ventricle and the velocity scale was decreased to <0.17 m/s. At this setting, the entire LV chamber was filled with aliased (mosaic) Doppler signals, while the motion of the surrounding LV walls was displayed as nonaliased (pure red-blue) Doppler signals. All images were manually traced and analyzed with a biplane Simpson's rule algorithm. End-diastolic and end-systolic volumes measured from color Doppler correlated well with those measured from 2-dimensional echocardiography ($r = 0.99$, standard error of the estimate [SEE] = 11.9 ml; $r = 0.99$, SEE = 4.4 ml, respectively) and cineangiography ($r = 0.92$, SEE = 16.8 ml; $r = 0.90$, SEE = 9.9 ml, respectively). Color Doppler EF correlated extremely well with that measured from 2-dimensional echocardiography ($r = 0.99$, SEE = 1.6%) and cineangiography ($r = 0.96$, SEE = 3.4%). Thus, EF can be accurately measured from the color Doppler examination.

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Comparison of Chest Pain, Electrocardiographic Changes and Thallium-201 Scintigraphy During Varying Exercise Intensities in Men with Stable Angina Pectoris

Gary V. Heller, MD, PhD, Imtiaz Ahmed, MD, Peter L. Tilkemeier, MD, Marilyn M. Barbour, PharmD, and Carol Ewing Garber, PhD

This study was performed to evaluate the presence of angina pectoris, electrocardiographic changes and reversible thallium-201 defects resulting from 2 different levels of exercise in 19 patients with known coronary artery disease and evidence of exercise-induced ischemia.

The exercise protocols consisted of a symptom-limited incremental exercise test (Bruce protocol) followed within 3 to 14 days by a submaximal, steady-state exercise test performed at 70% of the maximal heart rate achieved during the Bruce protocol. The presence and time of onset of angina and electrocardiographic changes (≥ 0.1 mV ST-segment depression) as well as oxygen uptake, exercise duration and pressure-rate product were recorded. Thallium-201 (2.5 to 3.0 mCi) was injected during the last minute of exercise during both protocols, and the images were analyzed using both computer-assisted quantitation and visual interpretations.

Incremental exercise resulted in anginal symptoms in 84% of patients, and electrocardiographic changes and reversible thallium-201 defects in all patients. In contrast, submaximal exercise produced anginal symptoms in only 26% ($p < 0.01$) and electrocardiographic changes in only 47% ($p < 0.05$), but resulted in thallium-201 defects in 89% of patients ($p =$ not significant).

The locations of the thallium-201 defects, when present, were not different between the 2 exercise protocols. These findings confirm the sequence of the ischemic cascade using 2 levels of exercise and demonstrate that the cascade theory is applicable during varying ischemic intensities in the same patient.

(Am J Cardiol 1991;68:569-574)

The temporal sequence of myocardial ischemia is thought to be initiated by alterations in blood flow or increased myocardial oxygen demand, or both, followed by dysfunction of the myocardium, electrocardiographic ST abnormalities, and finally angina pectoris.¹⁻³ This sequence, termed the "ischemic cascade," has led some investigators to propose that silent myocardial ischemia occurs in situations in which the ischemic insult is not sufficient to cause angina pectoris.⁴ Data supporting this model of ischemia have been obtained under conditions in which the individual events of the sequence can be separately observed by altering the severity and duration of the ischemia.^{1,5,6}

Whereas these studies have established the sequence of myocardial responses during 1 ischemic challenge, little information is available regarding the effects of varying physiologic conditions on the ischemic cascade. A recent study from our laboratory examined the relation between electrocardiographic changes and angina under markedly different exercise intensities in 33 patients with provokable ischemia.⁷ This study found that a lower work load yielded far less angina despite continued electrocardiographic changes in patients.

Although previous studies have demonstrated the effects of exercise intensity on clinical features of ischemia, little information regarding myocardial function or blood flow distribution is available. Thallium-201

From the Human Performance Laboratory, Division of Cardiology, Department of Medicine, Memorial Hospital of Rhode Island, Pawtucket, Rhode Island, and the Brown University Program in Medicine, Providence, Rhode Island. This study was supported by grants from the Rhode Island Foundations and from Dupont Radiopharmaceuticals. Manuscript received February 19, 1991; revised manuscript received and accepted May 13, 1991.

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imaging has been used as a marker of coronary blood flow that can identify both the presence and degree of ischemia.⁸⁻¹⁰ The present study was performed using thallium-201 imaging to evaluate the events of the ischemic cascade during varying levels of myocardial demand using both incremental and submaximal, steady-state exercise.

METHODS

Patients: All male patients referred for exercise thallium-201 studies at the Memorial Hospital of Rhode Island during a 2-year period were screened for inclusion in this study. Entry criteria included anginal symptoms during symptom-limited exercise testing, positive electrocardiographic response (horizontal or downsloping ST segment depression ≥ 0.1 mV), a reversible thallium-201 defect, previous angina pectoris, and consent to participate.

Patients with conduction defects or left ventricular hypertrophy on the electrocardiogram at rest, those receiving digoxin or other medications, or electrocardiographic changes at rest that precluded electrocardiographic interpretation were not included in the study. Coronary artery bypass graft surgery at any time, percutaneous transluminal coronary angioplasty or myocardial infarction during the interval between the identifying exercise test and the completion of the research protocol were also exclusion criteria. Women were excluded because so few were able to meet entry criteria from our laboratory.

Procedures: EXERCISE TESTING: After giving informed consent, the subjects completed 2 exercise tests. An incremental exercise test was administered first, followed 3 to 14 days later by a 20-minute submaximal steady-state exercise test. Both tests were performed in the fasting state and at the same time of day. The patients continued their prescribed cardiac medications on the days of testing and no medication changes were made in the interval between the 2 tests.

The incremental exercise test was symptom-limited using a standard Bruce protocol on a Marquette series 1800 treadmill.¹¹ Test termination criteria included ST segment depression ≥ 0.3 mV, progressive angina pectoris, volitional fatigue or other reasons to stop according to standard criteria.¹¹

The submaximal, steady-state test was performed on the same treadmill at a work load that elicited a heart rate of 70% of the peak heart rate (± 5 beats/min) attained during the incremental exercise test. This work load was determined by estimating the treadmill speed without grade which approximated the MET level at this heart rate during the incremental protocol. The submaximal test began at this work load with adjustments in speed or addition of a slight grade (2 to 4%) made as necessary during the first 3 minutes in

order to attain the target heart rate. The subject walked at this work load for 20 minutes unless there was a reason to stop according to the previously described test termination criteria.¹¹

Interpretation of the exercise tests was performed in a blinded fashion at the completion of the study. Interpreters included 2 members of the study team as well as a cardiologist not associated with the study.

PHYSIOLOGIC MEASUREMENTS: The electrocardiogram, heart rate, blood pressure, oxygen uptake and ratings of anginal pain (scale of 1 to 4 intensity) were monitored and the pressure-rate product was calculated during both tests. Heart rate was calculated as the mean of 10 R to R intervals. The ischemic electrocardiographic threshold was defined as the time at which horizontal or downsloping ST-segment depression ≥ 0.1 mV first appeared.¹¹ The anginal threshold was defined as the time of the onset of angina pectoris. The pressure-rate product was calculated as the product of the systolic blood pressure and heart rate.

Oxygen uptake was measured by indirect open-circuit calorimetry using a Douglas bag technique. Mixed expired gas samples were collected during the last 30 seconds of each minute during exercise and analyzed for fractional concentrations of oxygen and carbon dioxide (Ametek S-3A oxygen analyzer and Beckman LB-2 carbon dioxide analyzer). Before each test, the analyzers were calibrated with a gas with known concentrations verified by the micro-Scholander technique.¹² Expiratory volumes were measured using a heated digital pneumotach (Hewlett-Packard model no. 47303A). Calculations of oxygen uptake and derived variables were obtained using the equations of Consolazio et al.¹³

THALLIUM-201 IMAGING: For each exercise protocol, thallium-201 (2.5 to 3.0 mCi) was injected intravenously 1 minute before completion of the exercise. Imaging commenced 10 minutes after exercise in the standard planar views: anterior, 45° left anterior oblique and 70° left anterior oblique view. Patients returned 4 hours later for delayed images. Equipment used for this study was an Elscint Corporation large field-of-view gamma camera with an all-purpose parallel-hole collimator.

THALLIUM-201 INTERPRETATION: All thallium-201 studies were interpreted visually, using a Sudbury Systems ImageCenter computer system. The studies were read without knowledge of the patient or exercise protocol and included images from normal subjects and patients with coronary artery disease who were not part of this study. The coded studies were reviewed by 3 of the investigators and agreement was by consensus.¹⁴ The heart contour on each projection was divided into 5 segments, for a total of 15 segments. Each segment was evaluated using a 4-point scale (0 = normal, 1 = slight-

TABLE I Data Obtained at Peak Exercise During Incremental Exercise (Bruce protocol) and Submaximal Steady-State Exercise Testing in 22 Patients

	Exercise Test		p Value
	Incremental	Submaximal	
Exercise duration (min)	8.0 ± 2.4	19.5 ± 2.3	≤0.01
Treadmill speed (miles/hour)	3.2 ± 0.5	2.3 ± 0.8	≤0.05
Treadmill grade (%)	13.6 ± 1.3	1.0 ± 2.5	≤0.01
Heart rate (beats/min)	130 ± 16	100 ± 13	≤0.01
Systolic blood pressure (mm Hg)	172 ± 18	153 ± 14	≤0.05
Diastolic blood pressure (mm Hg)	90 ± 11	86 ± 6	NS
Rate-pressure product (beats/min, mm Hg)	22,357 ± 3,303	15,275 ± 2,718	≤0.01
Maximal $\dot{V}O_2$ (ml · kg ⁻¹ · min ⁻¹)	20.7 ± 4.0	12.7 ± 3.4	≤0.01
Angina pectoris (no. of pts.)	16	5	≤0.01
Patients with ST depression (no. of pts.)	19	9	≤0.05
Maximal ST depression (mm)	2.6 ± 0.9	1.7 ± 0.8	≤0.05
Patients with reversible TI-201 defects (no. of pts.)	19	17	NS

NS = difference not significant; TI-201 = thallium-201; $\dot{V}O_2$ = oxygen consumption rate.

ly diminished activity, 2 = moderate reduction in activity, and 3 = absent activity equivalent to background). This method has been previously validated for reproducibility.¹⁵ If ≥ 2 of the 15 segments had defects, the study was considered abnormal.¹⁶

In addition to visual, blinded interpretation, the planar views were subjected to computerized qualitative analysis, using the procedure of Maddahi¹⁷ and Areeda¹⁸ and their co-workers. This program uses a circumferential profile analysis of pixel counts and compares the patient data with those from a group of 32 patients with a very low probability of significant coronary artery disease. These analyses were performed independent of the visual interpretations. Comparisons between the visual data and computerized analysis of the same views were made with regard to the presence and location of defects. Discrepancies were resolved by either identification of artifact, such as breast attenuation, or by accepting the quantitative findings as correct. Disagreement between visual and computerized analysis was $<5\%$.

Statistical analyses: Statistical analyses were completed using a multivariate approach repeated-measures analysis of variance with the Biomedical Statistical Package, program 4V.¹⁹ Post hoc tests were applied when indicated using a Tukey HSD test.

RESULTS

Nineteen men (mean age \pm standard deviation 61 \pm 7 years) completed the study protocol. All patients had stable angina pectoris. Six had prior myocardial infarction. Thirteen patients (68%) were taking anti-ischemic medications, with 6 receiving combination therapy.

Data obtained at peak exercise during the 2 exercise protocols are listed in Table I. During submaximal exercise, the maximally achieved heart rate, systolic blood pressure, heart rate-blood pressure product and oxygen

uptake were significantly lower than those achieved during the incremental exercise. By protocol design, the 2 exercise protocols were also considerably different in work load achieved, and the exercise duration during steady-state exercise was significantly longer than with incremental exercise.

The prevalence of angina pectoris, significant electrocardiographic changes and reversible thallium-201 defects during the 2 exercise protocols are shown in Figure 1. During the Bruce protocol test, 16 of 19 patients (84%) had angina and all patients exhibited reversible thallium-201 defects and electrocardiographic abnormalities. In contrast, during the low-level, steady-state exercise, only 5 patients had angina (26 vs 84%, $p < 0.01$) and 9 patients had significant electrocardiographic changes (47 vs 100%, $p < 0.01$). However, with submaximal exercise, 17 patients still had reversible thallium-201 defects (89 vs 100%, $p =$ not significant).

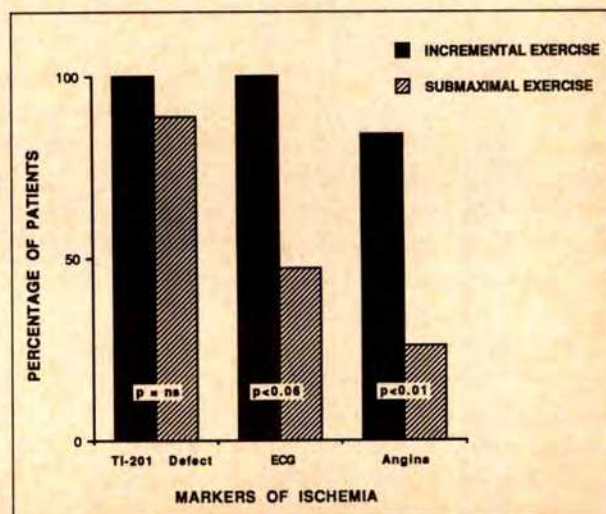


FIGURE 1. Comparison of prevalence of angina pectoris, electrocardiographic (ECG) changes and reversible thallium-201 (TI-201) defects during incremental exercise (Bruce protocol) and submaximal, steady-state exercise. ns = not significant.

TABLE II Comparison of the Onset of Anginal Symptoms During Incremental (Bruce protocol) Exercise and Submaximal, Steady-State Exercise

	Bruce (n = 5)	Submaximal (n = 5)	p Value
Time (min)	5.6 ± 2.4	9.3 ± 4.7	0.05
HR (beats/min)	115 ± 13	99 ± 3	0.05
SBP (mm Hg)	166 ± 17	147 ± 18	0.05
DBP (mm Hg)	89 ± 8	89 ± 5	NS
RPP (beats/min × mm Hg)	19,186 ± 3,296	14,590 ± 2,011	0.05
VO ₂ (ml · kg ⁻¹ · min ⁻¹)	17.1 ± 3.5	9.9 ± 2.2	0.05
Speed (miles/hour)	2.7 ± 0.8	2.0 ± 0.6	NS
Grade (%)	12.3 ± 1.8	0.0 ± 0.0	0.05

DBP = diastolic blood pressure; HR = heart rate; NS = not significant; RPP = rate-pressure product; SBP = systolic blood pressure; VO₂ = oxygen consumption rate.

TABLE III Comparison of the Onset of Electrocardiographic ST-Segment Changes (≥1 mm) During Incremental (Bruce protocol) Exercise and Submaximal, Steady-State Exercise

	Bruce (n = 9)	Submaximal (n = 9)	p Value
Time (min)	4.3 ± 2.1	7.3 ± 2.8	0.05
HR (beats/min)	112 ± 16	97 ± 13	0.05
SBP (mm Hg)	167 ± 11	150 ± 15	0.05
DBP (mm Hg)	90 ± 8	88 ± 6	NS
RPP (beats/min × mm Hg)	18,792 ± 3,222	14,564 ± 2,434	0.05
VO ₂ (ml · kg ⁻¹ · min ⁻¹)	16.6 ± 3.5	12.0 ± 3.7	0.05
Speed (miles/hour)	2.3 ± 0.6	2.4 ± 0.9	NS
Grade (%)	11.5 ± 1.5	0.6 ± 1.7	0.05

Abbreviations as in Table II.

The thallium-201 defects with incremental exercise were either partially (5 patients) or totally (14 patients) reversed on images 4 hours after exercise. Similarly, of the thallium-201 defects with submaximal exercise, all were either partially (6 patients) or totally (11 patients) reversed when imaged 4 hours later. The location of the scintigraphic abnormalities were similar between the 2 tests. Most defects affected the inferior and apical regions.

The 5 patients with angina during the low level protocol also had angina and electrocardiographic changes during incremental exercise. Each of these 5 patients had reversible thallium-201 defects during both protocols, and 4 had electrocardiographic changes with submaximal exercise. Although 9 patients had electrocardiographic changes with both protocols, the magnitude of the ST segment depression was significantly less with submaximal exercise (Table I).

In addition to evaluating the percentage of patients with evidence of ischemia, the onset of angina and electrocardiographic changes during both exercise protocols were examined (Tables II and III). Anginal pain that occurred in 5 patients during submaximal exercise began significantly later during exercise and at a significantly lower heart rate, rate-pressure product and oxygen consumption when compared with the onset of angina during incremental exercise (Table II). Similarly,

in the 9 patients with ischemic electrocardiographic changes during submaximal exercise, the onset was significantly later and was associated with lower heart rate, rate-pressure product and oxygen consumption when compared with that observed in the same patients during incremental exercise (Table III).

DISCUSSION

The present study was performed to evaluate the relations among 3 measures of ischemia during incremental and submaximal exercise in the same patients. With incremental exercise, all patients demonstrated significant electrocardiographic ST segment abnormalities and reversible thallium-201 defects, whereas 84% of patients developed angina. In contrast, with submaximal exercise only 26% of patients had angina, 47% had electrocardiographic changes, but 89% still developed reversible thallium-201 defects. The results of this study confirm the concept of the ischemic cascade.^{1,2} The sequence has been confirmed in numerous studies which demonstrate blood flow abnormalities early, followed by both systolic and diastolic dysfunction before clinical findings.²⁰⁻²²

Whereas previous studies described responses to a single ischemic stimulus, the present study evaluated the same patients under 2 conditions provoking ischemia with use of dissimilar exercise protocols. Assuming the ischemic sequence concept to be correct, one would expect the less strenuous protocol, which has a lower energy demand as well as lower myocardial oxygen demand, to produce less angina and fewer electrocardiographic changes than the more intense exercise. Since blood flow alterations have been proposed as one of the first events in the ischemic chain,² thallium-201 changes would be expected to be seen in a greater percentage of patients with lesser stress than would either electrocardiographic changes or angina. Not only do our findings demonstrate this, but the finding of a higher percentage of patients with reversible thallium-201 defects than patients with either angina or electrocardiographic changes provides a physiologic explanation for the greater sensitivity of thallium-201 imaging in detecting coronary artery disease, including low-level exercise.²³⁻²⁶

Currently, it has been assumed that the ischemic cascade follows a fixed threshold for each event, and that the degree of the ischemia influences only the presence or absence of the event. Our data suggest that although the ischemic cascade occurs in a set sequence in response to ischemia, the onset of each physiologic event varies in accordance with the level of ischemia. Thus, it is possible to hypothesize that the ischemic cascade may be conceived as a series of curves that respond to both the intensity and duration of the ischemia (Figure 2). For purposes of this hypothesis, ventricular

function has been added in addition to data supported by the present study on blood flow alterations, electrocardiographic and anginal assessments. Rapid, symptom-limited exercise may be expected to elicit all events in the cascade at an early time in the exercise period but at a high rate-pressure product. Moderately progressing maximal exercise would still bring about all changes, but at a longer time frame after the onset of exercise, and at a lower rate-pressure product. However, submaximal incremental exercise which intentionally limits the maximal activity would result in fewer patients exhibiting anginal symptoms or electrocardiographic changes. Finally, submaximal, steady-state exercise results in even fewer clinical events and at a reduced rate-pressure product.

These data also give further support to an energy expenditure relation between "silent" and symptomatic myocardial ischemia. Our data with submaximal exercise demonstrated that many patients who were previously symptomatic continued to show signs of ischemia (thallium-201 imaging, electrocardiographic changes) in the absence of symptoms. It has been suggested that patients with mixed anginal syndromes may have silent

ischemia in settings in which the work load or stress is not sufficient to cause angina pectoris. These episodes have been theorized to occur in daily situations, particularly with psychological stress or low-level activity.^{4,27-30} Two studies noted the onset of ambulatory ST segment depressions to be at a lower heart rate than that seen during laboratory conditions.^{4,29} This discrepancy in the onset of electrocardiographic changes is similar to our findings, and is likely explained by more gradual and prolonged exercise at a lower work load in the ambulatory setting (Figure 2). Although data from a study by Gasparetti et al³¹ did not show discrepancies between the time of onset of angina and electrocardiographic changes, they did confirm that patients had fewer anginal symptoms than electrocardiographic changes in the presence of thallium-201 defects.

The present study was undertaken with a group of patients with stable angina pectoris and evidence of ischemia from exercise tests. Thus, many were receiving antiischemic regimens. Therefore, the specific influence of any of these drugs on our results cannot be ascertained. All medications were held constant throughout the study for each patient, as was the time

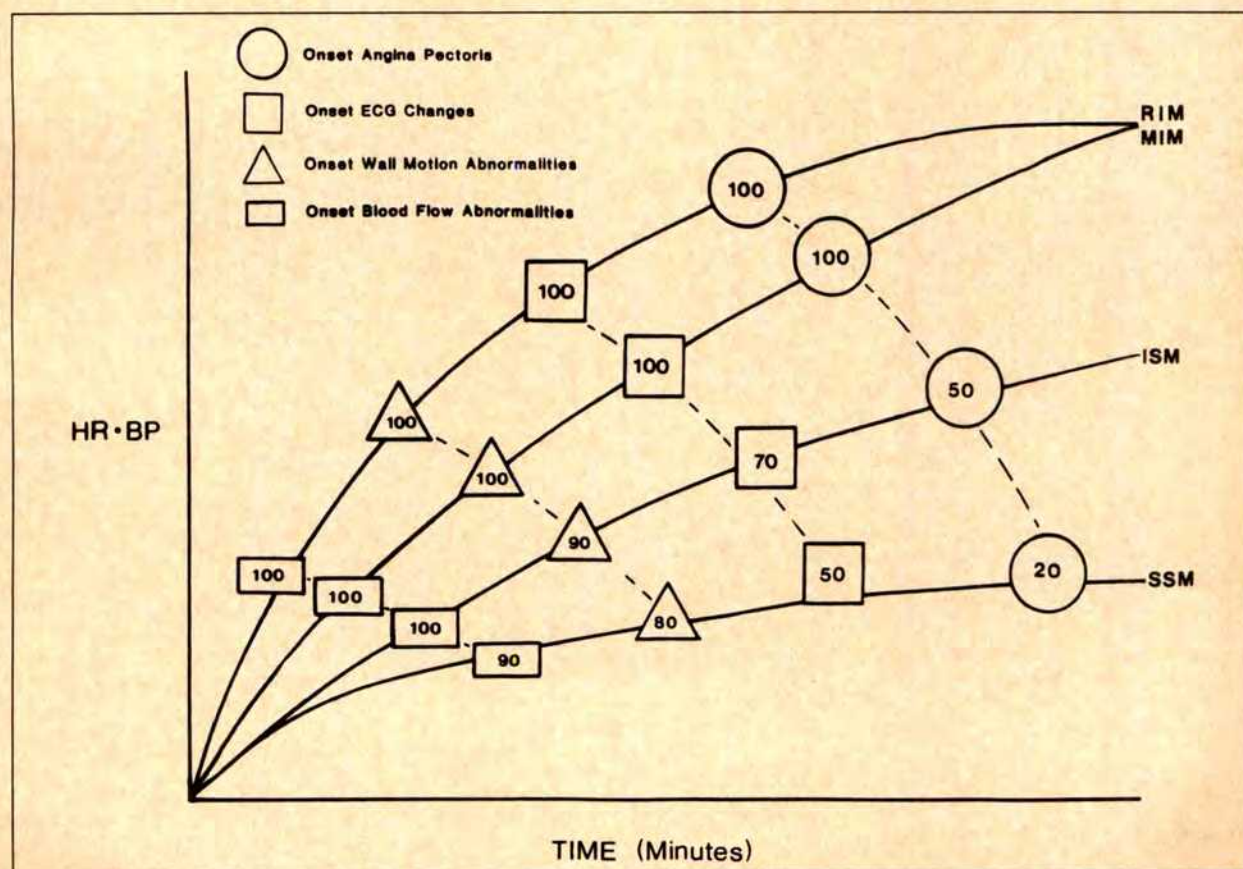


FIGURE 2. Theoretical relation between events of the ischemic cascade and intensity of exercise achieved. Three types of exercise are compared: maximal exercise, either with rapid or moderate incremental exercise (RIM, MIM); submaximal incremental exercise (ISM); and submaximal steady-state exercise (SSM). The relative onset of ischemic events may be compared with relation to time and either rate-pressure product or oxygen uptake. Rapid incremental exercise and submaximal steady-state exercise are based on results of the present study, whereas moderate or submaximal incremental exercise was theoretically derived from prior studies. BP = blood pressure; ECG = electrocardiographic; HR = heart rate.

frame between medication administration and exercise testing.

In conclusion, the results from the present study provide further support and extend the concept of the ischemic cascade during myocardial ischemia using a measure of blood flow during varying physiologic stress in the same persons. The results of this study suggest that, although angina or blood flow alterations may occur in a set sequence, the timing and hemodynamic level at the onset of the ischemic event varies with the physiologic stressor. Finally, these studies confirm that ischemia may occur at low levels of exercise in the absence of symptoms in the same patients who exhibit angina at higher exercise intensities.

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Usefulness of Technetium-99m-MIBI and Thallium-201 in Tomographic Imaging Combined with High-Dose Dipyridamole and Handgrip Exercise for Detecting Coronary Artery Disease

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Forty-two patients with known stable coronary artery disease, referred for coronary angiography, were examined with technetium-99m-hexakis-2-methoxy-2-methylpropyl-isonitrile (MIBI) tomography combined with a high-dose dipyridamole infusion (0.7 mg/kg) and handgrip stress. MIBI tomography was unable to show coronary artery disease only in 2 patients, thus yielding a sensitivity figure of 95%. MIBI tomography correctly identified 27 (82%) of 33 stenotic lesions ($\geq 50\%$ diameter stenosis) of the left anterior descending artery, 17 (61%) of 28 of those of the left circumflex artery, and 28 (90%) of 31 of those of the right coronary artery. The overall vessel sensitivity was 78%. The computed lumen diameter stenoses were more advanced in cases detected than in those not detected with MIBI tomography: 87 ± 14 vs $76 \pm 14\%$ ($p < 0.01$). The 50 to 69% stenoses did not show any tendency to produce less positive findings than those with $\geq 70\%$ stenoses. In the subgroup of 21 patients who also presented for thallium scintigraphy, the overall diseased vessel identification rate was 76% for thallium tomography and 83% for MIBI tomography ($p =$ not significant). Minor noncardiac side effects related to the dipyridamole-handgrip test occurred only in 5% of 63 study sessions.

A high-dose dipyridamole combined with isometric exercise is a safe stress method, and when used during scintigraphy, MIBI tomography is at least as efficient a tool as thallium tomography in detecting diseased vessel territories in patients in coronary artery disease.

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Technetium-99m, linked to hexakis-2-methoxy-2-methylpropyl-isonitrile (Tc-99m-MIBI), has been described as a myocardial perfusion imaging agent,¹ whose short half-life and a pure gamma emission enable the use of higher doses and thus, together with a higher photon energy, provides an image quality superior to that obtained using thallium. With only rare exceptions,² excellent agreement with thallium-images during single-photon emission computerized tomography, when combined with dynamic exercise, has been reported.³⁻⁵

Dipyridamole administration has been proposed as a feasible substitute for dynamic exercise in myocardial perfusion studies.⁶⁻⁸ Recently, planar imaging with Tc-99m-MIBI combined with dipyridamole infusion at the conventional dose of 0.56 mg/kg has been reported to be comparable to dynamic exercise studies, as well as to thallium-201 imaging and coronary angiography in a preliminary trial.⁹ The present study was designed to test the ability of Tc-99m-MIBI in the detection of uptake defects related to coronary artery stenoses verified by quantitative coronary angiography in patients with known coronary artery disease, and to compare its accuracy with thallium-201 when using a higher dose (0.7 mg/kg) of intravenous dipyridamole and handgrip isometric exercise as the stress method.⁶

METHODS

Patients: Forty-two patients (9 women, 33 men, aged 45 to 72 years) with typical angina pectoris (New York Heart Association class II to IV) but without other cardiac abnormalities, elective coronary angiography performed on 2 certain weekdays during a successive 21-week period, were included in the study after giving informed consent. MIBI tomography was performed in every patient, and thallium tomography in every second one. Twenty-six patients had had a previous Q-wave myocardial infarction. The protocol was approved by the ethical committee of the hospital.

Coronary angiography: A selective biplane coronary angiography in multiple projections, including cranial and caudal views, was performed by the Judkins technique. The stenoses of coronary arteries were quantified by the digitized draw-analysis of stenotic segments on

end-diastolic cine frames in 2 projections. The 35-mm film was projected on to a digitizing table and the borders of the stenosis; the vessel segments before and after the stenosis were traced from 2 projections and the results averaged. The correction of magnification was calculated with the aid of a reference grid and percent diameter stenosis was computerized as the result. Coronary luminal diameter reduction of ≥ 50 and $\geq 70\%$ were analyzed separately as significant lesions, including the major diagonal branch of the left anterior descending artery, major obtuse marginal branch of the left circumflex artery and posterior descending branch of the dominant right coronary artery.

Dipyridamole handgrip test: Dipyridamole was infused through a peripheral venous cannula at a rate of 0.175 mg/kg/min for 4 minutes, with a total dose of 0.70 mg/kg. One and one-half minutes after the end of dipyridamole infusion, the patients performed a handgrip exercise in a sitting position by squeezing a hand dynamometer at a force of 50% of mean maximal voluntary contraction for 1½ minutes. The intravenous isotope injection was given 1 minute before ending the squeezing. If severe symptoms developed or if blood pressure decreased >20 mm Hg, aminophylline, 50 to 100 mg, was administered, and in cases of anginal chest pain, sublingual nitroglycerin was given.

Thallium and Tc-MIBI tomography: The studies were performed according to the 1-day stress-rest principle,⁹ in random order, either before or after coronary angiography within the time domain of 3 months. Long-acting nitrates were discontinued on the day of examination. Medications did not change essentially between the scintigraphic examinations. The doses of thallium-201 and Tc-99m-MIBI were about 2.5 (90

MBq) and 8 mCi (300 MBq), respectively. The dose of Tc-99m-MIBI for the resting study, 3 to 4 hours later, was about 20 mCi (740 MBq).

Imaging data were acquired as a 64×64 matrix using the Siemens Rota™ ZLC/75 gamma camera with a low-energy, all-purpose collimator over 180° , starting from the 45° left posterior oblique projection, collecting 30 images every 6.0° for 35 seconds each, with a total acquisition time of 20 minutes.⁷ Each projection was corrected for nonuniformity with thallium-201 or Tc-99m flood image. A 15 or 25% energy window was used for Tc-99m and thallium-201, respectively. The transaxial sections were constructed by filtered backprojection with a Gamma-11 computer system using SPETS program (Shepp & Logan filter, number 4 in SPETS program). Coronal and sagittal slices were generated from the set of transaxial tomograms, corresponding to transverse and longitudinal sections of the cardiac axis, and stored with film formatter. As a quantitative analysis the circumferential profiles were calculated from the sum of 3 to 5 coronal slices for both rest and exercise study. Washout profile was also calculated for thallium, and rest/exercise profile for technetium studies. A bullseye analysis was performed in controversial cases (Figure 1).

Scintigraphs were interpreted independently by 2 observers who were not aware of the angiographic findings. Five discrete regions of the left ventricular myocardium—anterior, septal, apical, inferior and posterolateral—were defined. The regional perfusion was considered abnormal if a defect was visually present in ≥ 2 tomographic slices with or without redistribution. Complete agreement between the observers concerning the presence or absence of defects was reached in 38 of 42

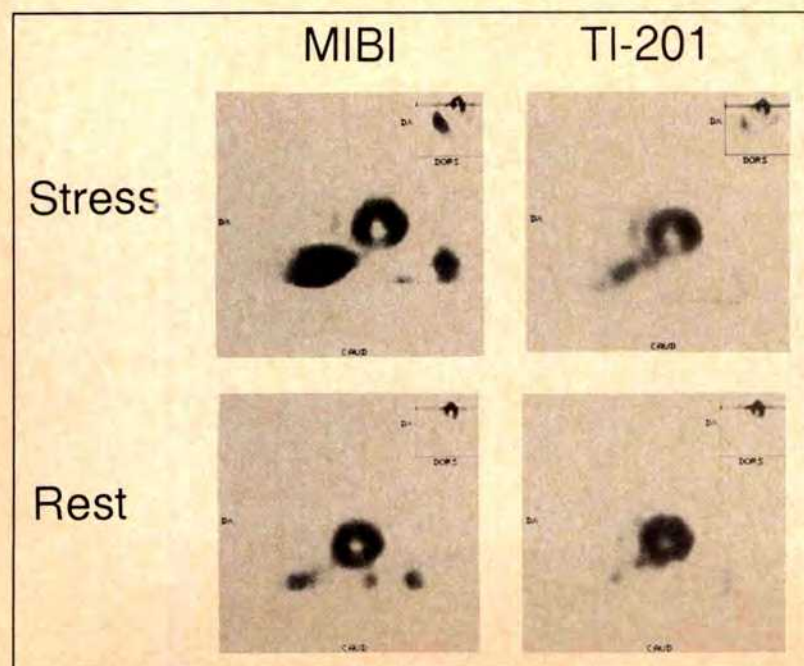


FIGURE 1. Hexakis-2-methoxy-2-methylpropyl-isonitrile (MIBI) (left) and thallium (TI-201) (right) tomography study on a patient with 87% stenosis in the distal right coronary artery (balanced dominance). Stress = dipyridamole infusion and handgrip exercise.

TABLE I Positive Findings on MIBI Tomograms in 42 Patients Compared with Findings in Individual Coronary Vessels on Coronary Angiograms

No. of Findings	Findings in Coronary Arteriograms (diameter stenosis)								
	Left Anterior Descending Artery			Left Circumflex Artery			Right Coronary Artery		
	0-49%	50-69%	70-100%	0-49%	50-69%	70-100%	0-49%	50-69%	70-100%
Angiography	9	9	24	14	2	26	11	7	24
MIBI defects									
Reversible	0	7	13	0	1	11	3	3	13
Fixed	0	1	6	0	0	5	0	2	10
Total	0	8	19	0	1	16	3	5	23
Scars									
LV angiography		11			5				15
MIBI		7			4				11
Vessel sensitivity		82%			61%				90%

LV = left ventricular; MIBI = hexakis-2-methoxy-2-methylpropyl-isonitrite; Scars = myocardial infarction scars proved by left ventricular cineangiography.

TABLE II Positive Findings on MIBI and Thallium Tomograms Compared with Findings in Individual Vessels on Coronary Arteriograms in 21 Patients

No. of Findings	Findings in Coronary Arteriograms (diameter stenosis)								
	Left Anterior Descending Artery			Left Circumflex Artery			Right Coronary Artery		
	0-49%	50-69%	70-100%	0-49%	50-69%	70-100%	0-49%	50-69%	70-100%
Angiography	6	3	12	7	1	13	4	4	13
MIBI									
Reversible	0	3	6	0	1	7	1	1	5
Fixed	0	0	4	0	0	2	0	2	7
Total	0	3	10	0	1	9	1	3	12
Thallium									
Reversible	1	1	9	0	1	6	1	0	5
Fixed	0	1	1	0	0	3	0	3	5
Total	1	2	10	0	1	9	1	3	10
Scars									
LV angiography		4			3				9
MIBI		3			2				7
Thallium		2			2				6

Abbreviations as in Table I.

cases (90%). Disagreement about the results was resolved by discussion.

Statistics: Results in patient study groups were expressed as mean \pm standard deviation. The normalcy rate was defined as the number of vessel territories with normal scintigraphic patterns divided by that of corresponding angiography findings. The significance among the mean values was tested by the Mann-Whitney U test, and among the paired group data by the McNemar test. A p value <0.05 was considered significant.

RESULTS

MIBI tomography revealed a normal perfusion scan only in 2 patients (1 with 1-vessel and 1 with 2-vessel disease), thus yielding a sensitivity of 95% in detecting coronary artery disease. From the stenotic lesions of left anterior descending artery, left circumflex artery and right coronary artery, MIBI tomography correctly demonstrated 82, 61 and 90%, respectively (Table I). These vessel sensitivity figures tended to remain lower

in the subgroup of 50 to 70% stenoses than in that of 70 to 100% stenoses, but only in the territories of left circumflex and right coronary arteries (Table I). The overall vessel disease sensitivity and specificity with MIBI tomography was 78 and 91%, respectively. MIBI tomography suggested false-positive findings (all 3 occasions of them in the territory of right coronary artery), and consequently the overall vessel normalcy rate was 91%. When the areas of the left circumflex and right coronary arteries were assessed in combination, MIBI tomography revealed 91% of the corresponding stenotic lesions observed in angiography. Left ventricular cineangiography showed 31 akinetic wall segments indicating myocardial infarction scars. MIBI tomography showed a corresponding fixed defect in 71% of these cases (Table I). When computed from data on the quantitative analysis of coronary arteriography, the mean stenosis observed with MIBI tomography (i.e., true-positive findings) was $87 \pm 14\%$ ($n = 72$) of the lumen diameter. The corresponding figure for stenoses

not detectable with scintigraphy (i.e., false-negative findings) was $76 \pm 14\%$ ($n = 20$) ($p < 0.01$).

In the subgroup of 21 patients submitted for both thallium and MIBI tomography, the overall diseased vessel identification rates were 83% for MIBI tomography and 76% for thallium tomography ($p =$ not significant, Table II). Coronary angiography demonstrated 5 patients with 1-vessel disease (4 of them had evidence on both the MIBI and thallium tomograms). Of the 16 patients with multivessel disease, 10 had correct diagnosis on MIBI tomography and 9 on thallium tomography.

Anginal chest pain occurred in 8 patients, electrocardiographic ST-segment depression in 3, and noncardiac symptoms (dyspnea or dizziness, or both) in 3 in the context of dipyridamole infusion or handgrip exercise, or both. Aminophylline, 50 and 100 mg, was injected on 2 occasions to abolish the symptoms. With regard to the 63 study sessions, the frequency of dipyridamole-related adverse events were: chest pain 13%, ST-segment depression 5%, and noncardiac side effects 5% (total 23%).

DISCUSSION

Dipyridamole-handgrip: The most distinctive feature of the design of the present study was the substitution of dynamic exercise by dipyridamole infusion and isometric handgrip exercise in conjunction with MIBI tomography. The use of dipyridamole infusion as a substitute for dynamic exercise has been previously validated by us⁷ and others¹⁰ in thallium studies. The method has even been suggested to be superior to dynamic exercise in detecting multivessel disease⁷ and redistribution defects with thallium scintigraphy.¹⁰

We administered a higher intravenous dose (0.7 mg/kg) of dipyridamole reported previously.¹¹ Irrespective of the severity of coronary artery disease and the withdrawal of long-acting nitrates on the day of examination, the rate of noncardiac side effects or ischemic pain after dipyridamole was not higher than that reported earlier with lower dipyridamole doses.^{6,11,12} The total range of adverse events remained considerably lower than in a large multicenter study reported recently by Ranhosky et al.¹³ However, prolonged severe myocardial ischemia, bronchospasm and even death have been reported¹⁴⁻¹⁷ and therefore, total doses of dipyridamole have been recommended not to exceed 60 mg.¹⁷ The efficacy of isometric handgrip exercise as an adjuvant coronary vasodilator has recently been questioned,^{8,18} but in our experience the low rate of dipyridamole-related side effects is probably due to the counteracting effect of isometric exercise on the decrease in blood pressure caused by dipyridamole, as well as to the day-long discontinuation of long-acting nitrates.

MIBI tomography: In the present study group with known coronary artery disease, the detection of the disease, per se, was not an essential question. The overall vessel disease sensitivity of 78% remained only slightly lower than in some recent studies including significantly less cases of 3-vessel disease,^{4,5,19} which certainly reduces the probability of "missing" individual hypoperfused vessel territories.³ Our series indicates that MIBI tomography is an efficient tool in detecting significant stenoses of the right coronary artery. The distinction between the stenoses of the right coronary and left circumflex arteries depends largely on how dominant these vessels are,²⁰ as evidenced in this study: the combined area of these arteries enhanced the rate of correctly identifying lesions.

MIBI versus thallium tomography: When assessing the subset of 21 patients submitted for both MIBI tomography and thallium tomography, the former appeared to offer a slight advantage in detecting vessel stenoses. This is in agreement with some recent studies on patients with angiographically proved coronary artery disease,^{21,22} but disagrees somewhat with results obtained with 38 patients by Kahn et al.,⁵ who suggested MIBI tomography to be superior to thallium tomography.

Diameter stenosis: We used computer-based quantitative analysis in determining the percent diameter magnitude of the stenoses. It has been suggested that "moderately severe" stenoses of 30 to 70% lead to restriction of "coronary flow reserve" in an unpredictable way.²³ In our data, the "borderline" stenoses of 50 to 70% did not appear to compromise perfusion essentially less than "critical stenoses," irrespective of the isotope used in scintigraphy.

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Efficacy of Slow-Release Nifedipine on Myocardial Ischemic Episodes in Variant Angina Pectoris

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To evaluate the efficacy of slow-release nifedipine (a single dose of 20 mg given at 10 P.M. or 2 doses of 20 mg at 10 P.M. and 6 A.M.) on ischemic episodes in patients with variant angina, a single-blind crossover study with ambulatory electrocardiographic monitoring was performed in 15 patients (13 men and 2 women, mean age 63 years). In all, there were 646 ischemic episodes detected with ambulatory electrocardiographic monitoring during the study period, and 618 episodes of them occurred during placebo periods with a circadian variation. Sixty-nine percent of the episodes in placebo periods were asymptomatic. The number of anginal attacks, nitroglycerin tablets taken, ST-segment elevation and the total ischemic duration significantly decreased during nifedipine therapy compared with results after the placebo therapy period, respectively ($p < 0.01$ or 0.05). Twenty-eight ischemic episodes occurred during nifedipine therapy when the plasma level of nifedipine was low. Thus, asymptomatic ischemic episodes more frequently occur than symptomatic episodes and the administration of slow-release nifedipine is highly effective in suppressing not only symptomatic but also asymptomatic myocardial ischemia in patients with variant angina. The timing of the administration of slow-release nifedipine is an important factor in suppressing ischemic episodes.

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Variant angina is characterized by recurrent attacks of chest pain occurring at rest and associated with ST-segment elevation on the electrocardiogram.¹ The attacks occur most frequently from midnight to early morning and it is now established that this syndrome is caused by spasm of a large coronary artery.²⁻⁶

For the treatment of this syndrome, the efficacy of calcium antagonists has been shown.⁷⁻⁹ However, the pattern of administration of calcium antagonists to patients with variant angina has not been examined critically. The half-life of nifedipine in a conventional capsule form is approximately 4 to 5 hours¹⁰ and it does not always suppress the myocardial ischemic episode in the early morning if administered in the daytime. Slow-release nifedipine is the alternative form of tablet containing nifedipine and the half-life of nifedipine is longer (10 to 15 hours)¹¹⁻¹³ than the capsule form.

The evaluation of the efficacy of drugs on variant angina must be based not only on symptomatic but also on asymptomatic ischemic episodes because many episodes in patients with variant angina are asymptomatic. Ambulatory electrocardiographic monitoring is a useful method for detecting myocardial ischemia in patients with various types of angina.¹⁴⁻¹⁹ In the present study, we evaluated the efficacy of slow-release nifedipine on both symptomatic and asymptomatic ischemic episodes in patients with variant angina by a single-blind crossover study using ambulatory electrocardiographic monitoring.

METHODS

Patients (Table I): Fifteen patients with variant angina (13 men and 2 women), aged 49 to 80 years (mean 63), were studied. All patients had recurrent anginal attacks associated with ST-segment elevation on the electrocardiogram. Ischemic attacks with ST-segment elevation appeared in the anterior leads in 7 patients, in the inferior leads in 3 patients and sometimes in the anterior leads and other time in the inferior leads in 5 patients. Spasm of a major coronary artery perfusing the area, represented by ST-segment elevation, was documented by coronary angiography during a spontaneous attack or an attack induced by intracoronary injection of acetylcholine in all patients but 1. Coronary angiography could not be performed in 1 patient be-

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TABLE I Clinical Data of the Patients

Pt. No.	Age (yr) & Sex	ECG Change During Attack	Coronary Angiogram	
			During Attack	After Nitroglycerin
1	49F	ST ↑ in V ₁₋₄	Seg. 7; 100%	Significant stenosis (—)
2	72M	ST ↑ in V ₂₋₅	Seg. 7; 100%	Seg. 1; 75%
3	62M	ST ↑ in II, III, aVF	Seg. 2; 90%	Significant stenosis (—)
4	59M	ST ↑ in II, III, aVF, V ₁₋₃	Seg. 1; 90%	Seg. 13; 75%
5	63M	ST ↑ in II, III, aVF, V ₁₋₆	Seg. 6; 75%	Significant stenosis (—)
6	59M	ST ↑ in II, III, aVF	Seg. 1; 100%	Significant stenosis (—)
7	57M	ST ↑ in II, III, aVF	Seg. 7; 100%	Significant stenosis (—)
8	80M	ST ↑ in II, III, aVF, V ₁₋₆	Seg. 7; 100%	Seg. 7; 90%
9	59M	ST ↑ in I, aVL, V ₁₋₆	RCA; ?	Significant stenosis (—)
10	63F	ST ↑ in V ₁₋₄	Seg. 7; 99%	Seg. 6; 90%
11	63M	ST ↑ in V ₁₋₄	Seg. 6; 100%	Seg. 7; 90%
12	71M	ST ↑ in V ₂₋₅	Seg. 7; 100%	Seg. 7; 90%
			Seg. 12; 100%	Seg. 4; 90%
				Seg. 7; 75%
				Seg. 12; 95%
13	80M	ST ↑ in II, III, aVF, V ₅₋₆	CAG; ?	Significant stenosis (—)
14	51M	ST ↑ in II, III, aVF, V ₁₋₄	Seg. 1; 100%	
			Seg. 7; 90%	
			Seg. 11; 100%	
15	55M	ST ↑ in I, aVL, V ₁₋₄	Seg. 7; 100%	Seg. 7; 75%
				Seg. 14; 75%

CAG = coronary angiogram; ECG = electrocardiogram; LCA = left coronary artery; RCA = right coronary artery; Seg. = segment; ↑ = elevation; ? = not performed.

cause of age and clinical condition. The details of the method of the induction of coronary spasm have been reported.^{20,21} Informed consent was obtained from each patient.

Protocol: All medication except for sublingual nitroglycerin was stopped ≥ 2 days before the study. Because the attacks of variant angina are often unstable and may result in acute myocardial infarction or sudden cardiac death, a double-blind study was avoided and a single-blind crossover study was performed for 16 days. Four successive periods were designed as follows: placebo I period—when placebo was given orally once a day at 10 P.M. for 4 days; nifedipine I period—when slow-release nifedipine, 20 mg was given at 10 P.M. for 4 days; placebo II period—when placebo was given twice a day at 10 P.M. and 6 A.M. for 4 days; and nifedipine II period—when slow-release nifedipine, 20 mg, was given twice a day at 10 P.M. and 6 A.M. for 4 days. Patients were instructed to maintain a daily diary and to describe the episodes of anginal attack if they noticed the symptoms.

Ambulatory electrocardiographic monitoring: During the last 2 days of each period, 48-hour ambulatory electrocardiographic monitoring (Del Mar Avionics Electrocardiocoder, model 447) was performed and analyzed with the use of the Evaluator II (Del Mar Avionics, model 9500A). Two channels of bipolar precordial leads were arranged so that one could represent the zone of myocardial ischemia previously proved and the other the opposite zone. Myocardial ischemia due to coronary spasm was defined as transient ST-segment

elevation ≥ 0.2 mV compared with the baseline ST level at a point 60 ms after the nadir of the S wave. ST-segment changes considered to be due to postural change, such as sudden, sustained ST-segment changes or those accompanied by an abrupt change of the QRS complex, were strictly excluded. These analyses were performed by >2 observers.

Blood sampling: Blood sampling was performed on the last day of the nifedipine II period to measure plasma levels of nifedipine. The timing of the sampling was 30 minutes before, and 30 minutes and 1, 2, 4, 6, 8 and 12 hours after the administration of slow-release nifedipine, 20 mg, at 10 P.M. The plasma level of nifedipine was measured by high-performance liquid chromatography.

Statistical analysis: The results are expressed as mean \pm 1 standard error. Analysis of variance (repeated measures) was used to compare the differences of parameters between each period. A *p* value <0.05 was considered significant.

RESULTS

Anginal attack: The number of anginal attacks was 14 ± 5.0 , 1.8 ± 0.5 , 14.1 ± 8.1 and 0.8 ± 0.5 times in the placebo I, nifedipine I, placebo II and nifedipine II periods, respectively. It decreased significantly during the nifedipine I and II periods ($p < 0.05$) compared with that during the placebo I period. It also decreased significantly during the nifedipine II period ($p < 0.05$) compared with that during the placebo II period. Slow-release nifedipine suppressed the attacks completely in

6 of 15 patients during the nifedipine I period and in 11 of 15 patients during the nifedipine II period.

Consumed nitroglycerin tablet: The number of consumed nitroglycerin tablets was 5.3 ± 1.4 , 1.3 ± 0.5 , 4.2 ± 1.9 and 0.1 ± 0.1 tablets in the placebo I, nifedipine I, placebo II and nifedipine II periods, respectively. It decreased significantly during the nifedipine I ($p < 0.05$) and nifedipine II ($p < 0.01$) periods compared with the number during the placebo I period. It also decreased significantly during the nifedipine II period ($p < 0.05$) compared with that during the placebo II period. Eight of 15 and 13 of 15 patients did not consume nitroglycerin tablets during the nifedipine I and nifedipine II periods, respectively.

Number of ischemic episodes detected by ambulatory electrocardiography: There were 646 ischemic episodes detected with ambulatory electrocardiographic monitoring during this study, and 618 episodes of them occurred during placebo periods. Four hundred and twenty-five of 618 episodes (69%) was asymptomatic. The number of ischemic episodes was 24.9 ± 7.4 , 1.7 ± 1.3 , 16.3 ± 6.8 and 0.1 ± 0.1 times per 48 hours in the placebo I, nifedipine I, placebo II and nifedipine II periods, respectively (Figure 1). It decreased significantly during the nifedipine I and II periods ($p < 0.01$) compared with the number during the placebo I period. It also decreased significantly during the nifedipine II period ($p < 0.01$) compared with the number during the placebo II period. Nifedipine completely suppressed

ischemic episodes in 12 of 15 and in 13 of 15 patients during the nifedipine I and II periods, respectively. Figure 2 shows the number of symptomatic and asymptomatic episodes per quarter of a day. There was a circadian variation with a peak incidence from midnight to early morning; 40% of the total ischemic episodes appeared from 0 A.M. to 6 A.M.. Slow-release nifedipine not only suppressed the number of ischemic episodes from 618 to 28 (or to 5%) but also eliminated the circadian variation. The drug markedly suppressed asymptomatic as well as symptomatic episodes during the nifedipine I and II periods compared with the placebo I and II periods.

Duration of ST-segment elevation: Total duration of ST-segment elevation was 71.6 ± 18.6 , 3.9 ± 2.7 , 42.9 ± 16.3 and 0.5 ± 0.4 minutes per 48 hours in the placebo I, nifedipine I, placebo II and nifedipine II periods, respectively (Figure 3). It decreased significantly during the nifedipine I and II periods ($p < 0.01$) compared with the duration during the placebo I period. It also decreased significantly during the nifedipine II period ($p < 0.01$) compared with the placebo II period.

Plasma level of nifedipine: The plasma level of nifedipine was 24.0 ± 4.3 , 31.1 ± 6.6 , 52.7 ± 10.8 , 72.7 ± 12.3 , 93.0 ± 9.4 , 91.1 ± 10.2 , 67.3 ± 7.8 and $37.9 \pm$

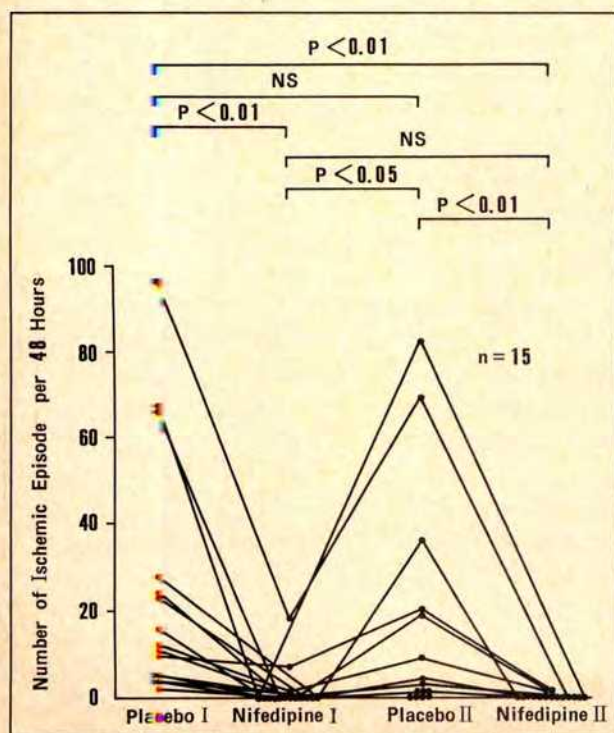


FIGURE 1. The effect of slow-release nifedipine on the number of ischemic episodes detected by 48-hour ambulatory electrocardiography. NS = not significant.

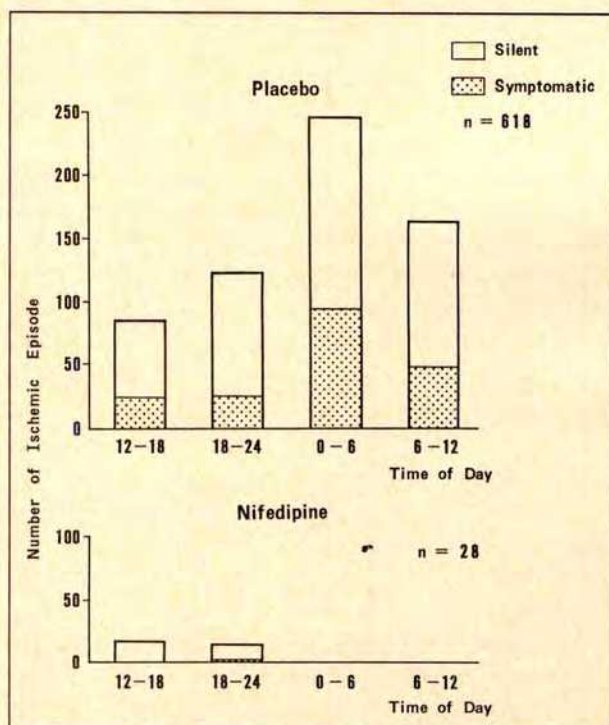


FIGURE 2. The number of symptomatic and asymptomatic episodes per quarter of a day during placebo (upper panel) and nifedipine (lower panel) periods. Forty percent of ischemic episodes occurred from 0 A.M. to 6 A.M., and there was a circadian variation. Slow-release nifedipine not only suppressed the number of ischemic episodes but also eliminated the circadian variation. Nifedipine markedly suppressed silent as well as symptomatic episodes during the nifedipine period compared with the placebo period.

5.6 ng/ml at baseline, 30 minutes, and 1, 2, 4, 6, 8 and 12 hours after administration, respectively (Figure 4). The plasma concentration reached a peak at 2 to 6 hours after the administration of the drug.

No adverse effects were noted in the present study.

Timing of the administration and ischemic episode:

Twenty-six ischemic episodes in 3 patients occurred from 5:08 P.M. to 10:53 P.M. during the nifedipine I period, and all of them were asymptomatic. During the nifedipine II period, only 2 episodes occurred in 2 patients. One of them occurred at 10:01 P.M., and the plasma concentration at 10 P.M. in this patient was very low, i.e., 7.3 ng/ml. Another occurred at 10:19 P.M., and the plasma concentration at 10 P.M. in this patient was 19.2 ng/ml. When 1 more slow-release nifedipine tablet was added at 6 A.M., the episodes between 5 P.M. and 10 P.M. were suppressed.

DISCUSSION

Efficacy of slow-release nifedipine on the ischemic episodes in variant angina: It is known that calcium antagonists are effective in the treatment of variant angina. Nifedipine is the prototypical agent, and the beneficial effects of the drug on the treatment of variant angina has been extensively documented.^{7,8} However, the half-life of nifedipine in a conventional capsule form is approximately 4 to 5 hours¹⁰ and it does not always

suppress the myocardial ischemic episode in the early morning if the drug is administered in the daytime. Slow-release nifedipine has been reported to have a longer half-life (10 to 15 hours).¹¹⁻¹³ Thus, slow-release nifedipine may be able to suppress ischemic episodes for a longer time than the conventional form. The plasma level of nifedipine in this study reached a peak level at 2 to 6 hours after the administration and remained elevated for 12 hours.

The present study shows that slow-release nifedipine, 20 mg, given twice a day at 10 P.M. and 6 A.M., or once a day given at 10 P.M. markedly suppressed both the number of anginal attacks and the number of nitroglycerin tablets taken. Furthermore, the drug also markedly suppressed both the number of ischemic episodes and the total duration of ST-segment elevation evaluated by ambulatory electrocardiographic monitoring. The drug suppressed asymptomatic as well as symptomatic episodes.

Relation between timing of the administration and the occurrence of ischemic episodes: It is interesting that even the administration of slow-release nifedipine once a day at 10 P.M. completely suppressed the ischemic episode from 11 P.M. to 5 P.M., probably because the plasma level of nifedipine increased enough to suppress ischemic episodes during this time zone. All of the episodes in the nifedipine I period were asymptomatic and occurred between 5 P.M. and 11 P.M., when the plasma levels of nifedipine seemed to be low. The ischemic episode disappeared completely in 13 of the 15 patients during the nifedipine II period, and only 2 episodes occurred in 2 patients during that period, at 10:01 and

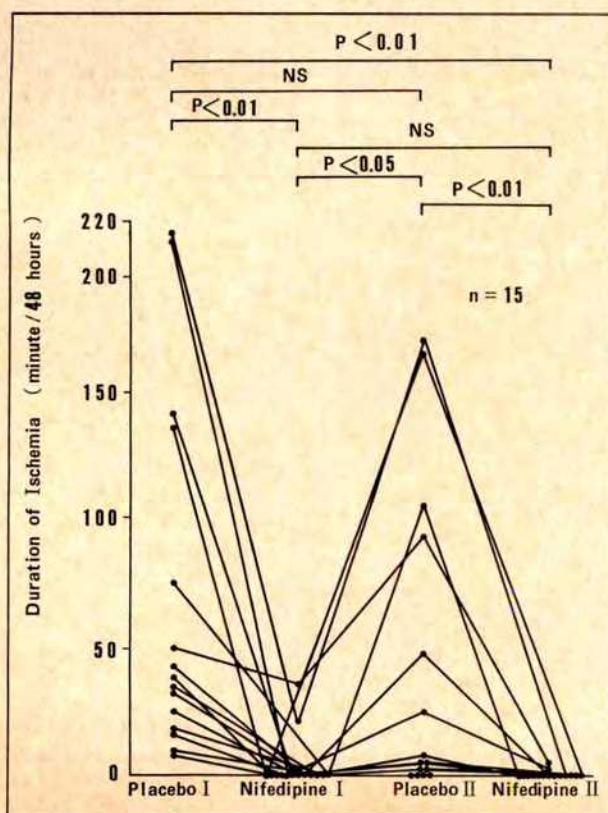


FIGURE 3. The effect of slow-release nifedipine on the duration of ischemic episodes detected by 48-hour ambulatory electrocardiography. NS = not significant.

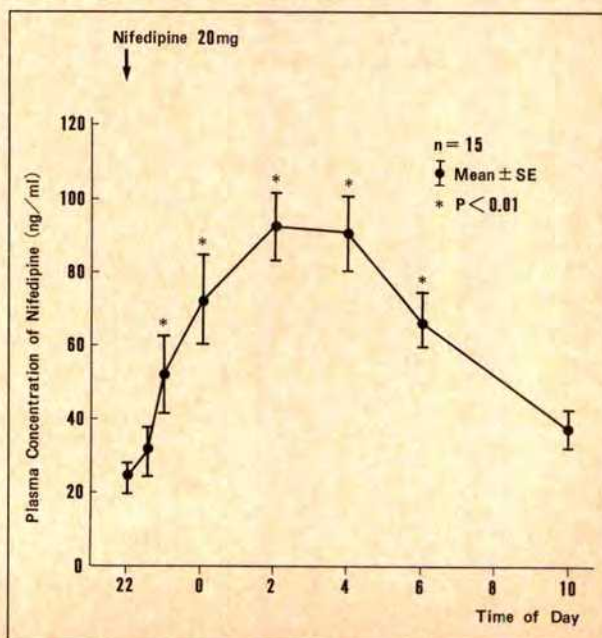


FIGURE 4. Plasma levels of nifedipine. Slow-release nifedipine, 20 mg, was administered at 10 P.M. (arrow). SE = standard error.

10:19 P.M., when the plasma level of the drug was low. These results strongly suggest that the ordinary and conventional pattern of drug administration may not adequately protect patients with variant angina against myocardial ischemia during the time when they are most vulnerable: from midnight to early morning. Conversely, the administration even once a day at 10 P.M. may be able to suppress most episodes.

We conclude that the administration of slow-release nifedipine, 20 mg, once a day at 10 P.M. or twice a day at 10 P.M. and 6 A.M. is highly effective in suppressing not only symptomatic but also asymptomatic myocardial ischemia in patients with variant angina. The timing of the administration of slow-release nifedipine is one of the important factors in suppressing ischemic episodes.

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Comparison of Intravenous Urokinase Plus Heparin Versus Heparin Alone in Acute Myocardial Infarction

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In a randomized trial of the effects on in-hospital mortality of intravenous urokinase plus heparin versus heparin alone, 2,531 patients with acute myocardial infarction in 89 coronary care units were enrolled for >30 months. Patients admitted within 4 hours of the onset of pain were randomized to receive either intravenous urokinase (a bolus dose of 1 million U repeated after 60 minutes) plus heparin (a bolus dose of 10,000 U followed by 1,000 IU/hour for 48 hours) or heparin alone (infused at the same rate). Complete data were obtained in 2,201 patients (1,128 taking urokinase and 1,073 taking heparin). At 16 days, overall hospital mortality was 8% in the urokinase and 8.3% in the heparin group ($p =$ not significant). Among patients with anterior infarction, mortality was 10.3% in the urokinase and 13.9% in the heparin group ($p = 0.09$; relative risk = 0.73). The incidence of major bleeding (urokinase 0.44%, heparin 0.37%) as well as the overall incidence of stroke (urokinase 0.35%, heparin 0.20%) was similar in the 2 groups. The rates of major in-hospital cardiac complications (reinfarction, postinfarction angina) were also similar.

(Am J Cardiol 1991;68:585-592)

Several randomized studies have shown that thrombolytic therapy may reestablish flow in the infarct-related artery,¹⁻⁴ preserve myocardial function⁵⁻⁷ and reduce mortality.⁸⁻¹⁵ However, there has been considerable debate over the choice of thrombolytic agent. Previous studies evaluating intravenous urokinase reported an impressive coronary thrombolysis,¹⁶⁻¹⁹ similar to that achieved with recombinant tissue-type plasminogen activator.¹⁶ Despite these potentially important findings, the effects of intravenous urokinase on the incidence of mortality have not been assessed in a large controlled trial. Accordingly, a controlled, multicenter trial with central randomization was begun in June 1985.

METHODS

Objectives of the Study: The primary endpoint was to compare the effects of intravenous urokinase plus heparin versus heparin alone, when infused within 4 hours after the onset of symptoms of myocardial infarction, on the incidence of mortality at 16 days.

The secondary end points were to assess the tolerability of the treatment regimen, with special emphasis on detecting bleeding complications, and to compare the effects of intravenous urokinase and heparin on the incidence of nonfatal cardiac events. All end points were established prospectively.

Sample size and randomization: The necessary sample size was estimated to be 1,500 patients for each arm of the study on the basis of the following assumptions: total early mortality of 12% in the control group and 10% in the urokinase group, type I (α) error of 0.05, and type II (β) error of 0.80. Inclusion was planned to be completed within 2 years. Since the assumed mortality turned out to be overestimated, after 2 years the steering committee decided to extend the inclusion period. The participating departments could only agree to increase the inclusion period for another half year.

To encourage recruitment, the trial procedures were as simple as possible—randomization involved only a telephone call and no forms. As a result, 89 hospitals randomized a total of 2,531 patients. Entry to the study was by 24-hour telephone service, based in the coronary unit of Novara. Before randomization the following information was recorded (on computered-general ran-

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*See appendix for participating centers and USIM investigators.

domization lists): patient identifiers, age and sex, time of the telephone call, blood pressure, hours from onset of the episode of pain that led to admission, electrocardiographic findings. After allocation of a specific treatment, the patient was irrevocably in the trial for an "intention to treat" analysis. The protocol specified 1 interim analysis every 500 randomized patients. Results from these were presented only to the review committee; a difference in mortality exceeding 3 standard deviations would have led the committee to call an early halt to the trial.

Eligibility: Patients of either sex were considered for randomization without age limitations. Criteria for eligibility were: typical chest pain refractory to sublingual nitroglycerin administration lasting ≥ 30 minutes, a maximum of 4 hours between onset of symptoms and recruitment, and ST-segment shift ≥ 0.1 mV in the peripheral leads of the electrocardiogram or ≥ 0.2 mV in the chest leads. As in previous studies,⁹ this research protocol did not require informed consent, mainly because the patients' predicament was judged too acute for acceptable application of the procedure. The medical staff was ready to provide explanations to the patients on request. Exclusion criteria were those adopted in the Gruppo Italiano per lo studio della Streptochinasi nell' Infarto Miocardico (GISSI) trial.⁹ Patients were also excluded if they lived in a foreign country or far away from the admitting hospital for adequate follow-up (administrative reasons).

Treatment: Patients were randomized to receive either 1 million U of urokinase (intravenous bolus), repeated after 50 minutes, plus 10,000 IU of intravenous heparin, or 10,000 IU of intravenous heparin alone.

Subsequently, a heparin infusion was begun in both treatment groups at a rate of 1,000 IU/hour and continued for 48 hours. After approximately 10 hours, the dose was adjusted to maintain the thrombin or partial thromboplastin time at 2 to 3 times control. After the second day of therapy, physicians were free to use oral anticoagulant drugs, or aspirin, or subcutaneous calcium heparin.

A 12-lead electrocardiogram was recorded before and 4, 24 and 48 hours after treatment. Blood samples for cardiac enzymes determination were obtained every 4 hours for the first 48 hours.

Discharge: At discharge, a prerandomization electrocardiogram and a simple single-side form were returned to the trial office. This "discharge form" provided further identifiers to assist central mortality follow-up after discharge, as well as brief details of compliance with study treatments in the hospital, any apparent adverse effect of treatment, and major events in the hospital (bleeding, recurrent myocardial ischaemia, reinfarction, cardiac arrest, heart failure, arrhythmias, stroke and death). All deaths were reviewed without knowledge of treatment allocation by the trial coordinator. Causes of death were subdivided into cardiac (i.e., definitely or possibly cardiac) and noncardiac. This latter includes all deaths attributed to cerebral, hemorrhagic and other vascular causes. For all reports of stroke on the discharge forms, further clinical and investigational details (including computerized tomographic scans) were requested.

Statistical analysis: Where appropriate, the statistical significance of differences was assessed with the chi-square test. Results are also presented in terms of rela-

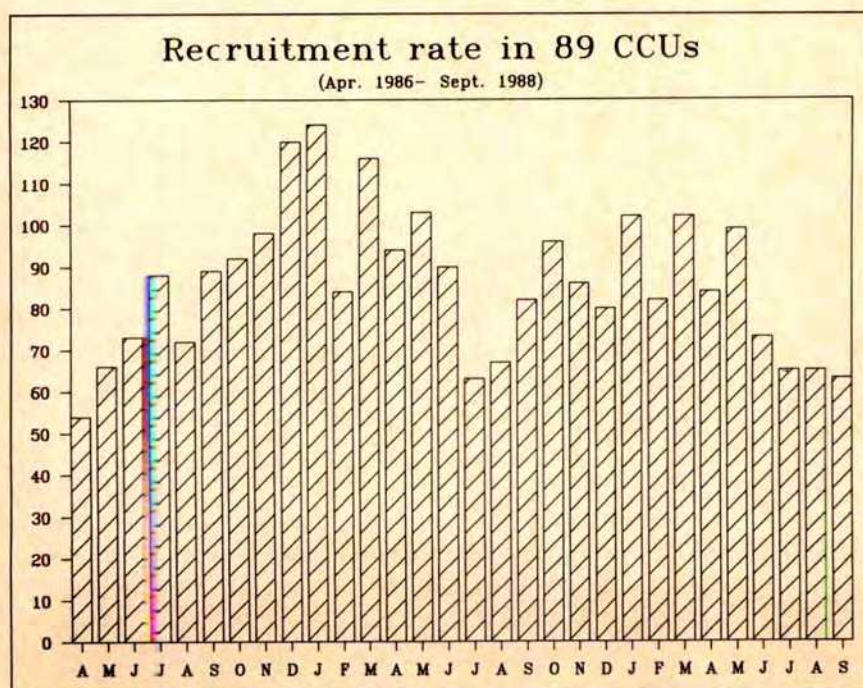


FIGURE 1. Recruitment rate in participating clinical centers. Letters are the initials of months. CCUs = coronary care units.

tive risk estimates and their 95% confidence intervals by using Haldane-Ancombes's correction for continuity for relative risk and Cornfield's "ricorsivo" method for confidence intervals.

Operational aspects: All data were collected on standardized forms which were first reviewed by the review committee and then processed, edited and analyzed in the Biomedical Research Institute A. Marxer S.p.A. (Ivrea, Italy).

The Review Committee regularly reviewed the otherwise confidential interim results. All deaths, nonfatal cardiac events, bleeding complications and other possible adverse effects were reviewed and classified by the trial coordinator.

RESULTS

Patients were randomized for >30 months (April 1986 to September 1988). Recruitment was steady, at a rate of about 80 patients per month (Figure 1). In all, 7,598 patients were screened (Figure 2), of whom 5,067 (66.7%) were not randomized. The reasons for exclusion as reported in the logs are shown in Figure 2 and their characteristics are summarized in Table I. Of the 2,531 patients entered into the study, 1,274 were assigned to the urokinase group and 1,257 to the heparin group. Three hundred thirty patients (184 control subjects and 146 patients receiving urokinase) were subsequently excluded from the analysis because myocardial infarction was not confirmed (59 control subjects, 47 patients receiving urokinase) or discharge forms had not yet been obtained by January 1989. The baseline characteristics, collected at randomization, of "missing" patients (224 patients, 8.8% of the total, 101 assigned to urokinase, 123 to heparin) closely corre-

TABLE I Baseline Characteristics of Patients on Admission to Coronary Units During Study Period but Not Randomized (5,067)

	Proportions (%)
Men	85
Age (years)	
≤ 70	58.7
> 70	41.3
Deaths	15.2

spond to those of the sample analyzed. Treatment was interrupted in 30 patients (11 control subjects and 19 taking urokinase). Causes of treatment interruption included low plasma fibrinogen (13 patients), sudden development of complicated ventricular fibrillation (15 patients) and severe hypotension (2 patients).

Table II lists the distribution of selected baseline characteristics. Overall, there was an excellent balance between the 2 groups, except for sex, non-Q-wave infarction and pulmonary edema. Throughout the first 16 days of the trial there was no major difference between the 2 groups with regard to ancillary therapy (Table III).

Mortality: The results presented in this report refer to the in-hospital period only, which was 9 to 16 days for >90% of patients and the same for the 2 groups. In the first 16 days after randomization, 90 patients (8%) in the urokinase group and 89 (8.3%) in the heparin group died. There was no significant difference in mortality rates between the 2 treatment groups. Mortality data are presented according to cause in Table IV. Table V lists the results for the entire population stratified by hours elapsed before randomization, age and site of infarct. Of the 596 patients treated with urokinase

FIGURE 2. Registry log of patients screened for the trial. CCUs = coronary care units; MI = myocardial infarction.

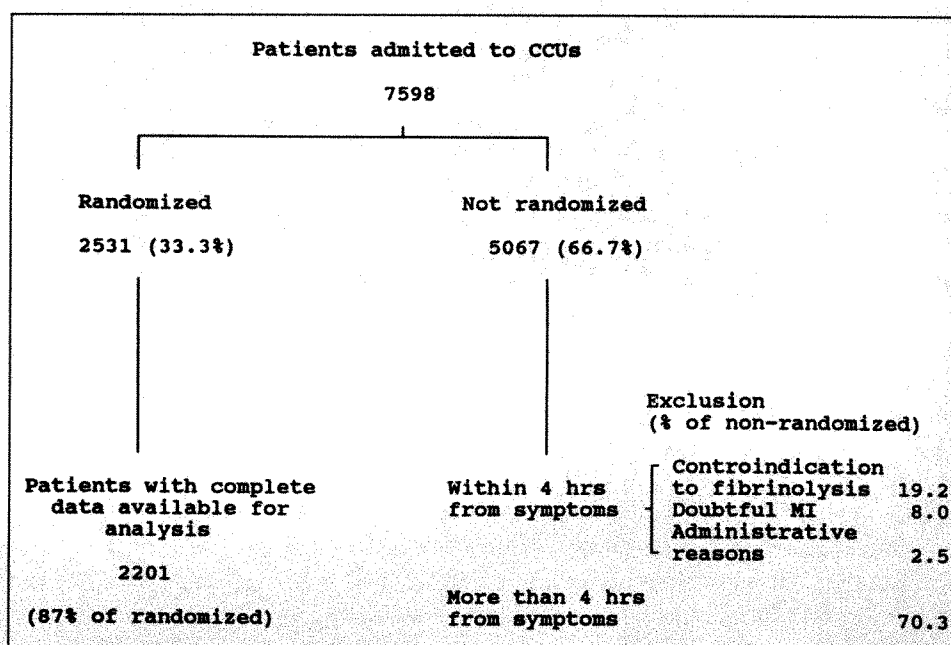


TABLE II Baseline Characteristics of Randomized Population

	Control Group (n = 1,073)		Urokinase Group (n = 1,128)		p Value
	No. of Pts.	(%)	No. of Pts.	(%)	
Men	863	(80.4)	952	(84.4)	p = 0.0168
Age (years)					
≤ 40	42	(3.9)	58	(5.1)	
41–60	493	(45.9)	523	(46.4)	
61–80	507	(47.2)	526	(46.6)	
> 80	31	(2.9)	21	(1.9)	
Time from onset of symptoms to ran- domization (hours)					
< 1	154	(14.3)	144	(12.8)	p = 0.042
1–2	384	(35.8)	452	(40.1)	
2–3	351	(32.7)	333	(29.5)	
3–4	178	(16.6)	192	(17.0)	
Systolic BP	931	(86.8)	985	(87.3)	
> 105 mm Hg					
Diastolic BP	805	(75.0)	835	(74.0)	
< 90 mm Hg					
Medical history					
Myocardial infarction	155	(14.4)	148	(13.1)	
Effort angina	109	(17.7)	203	(18.0)	
Rest angina	202	(18.8)	189	(16.7)	
Unstable angina	142	(13.2)	157	(13.9)	
Conditions at random- ization					
Arrhythmia	259	(24.1)	288	(25.5)	
Basilar moistales	203	(18.9)	229	(20.3)	
Pulmonary edema	4	(0.4)	17	(1.5)	p = 0.012
Shock	30	(2.8)	41	(3.6)	
Site and type of infar- ction					
Anterior	439	(40.9)	496	(44.0)	
Inferior	500	(46.6)	541	(48.0)	
Non-Q-wave	134	(12.5)	91	(8.0)	p = 0.0008

BP = blood pressure.

within 2 hours of the onset of symptoms, 45 (7%) died, compared with 42 of 538 (7.8%) in the heparin group. The difference in mortality was not statistically significant. There was a trend toward a higher mortality rate among control subjects with anterior wall infarctions in the heparin group, although the difference was not significant (relative risk = 0.73, confidence interval 0.48 to 1.10; p = not significant [NS]). However, patients with inferior wall infarcts who took urokinase had a significantly worse outcome than patients taking heparin (5.8 vs 2.2%; p = 0.04).

Nonfatal cardiac events (Table VI): Overall, ischemic events were comparable between the 2 groups. Reinfarctions in the hospital were reported to occur slightly (not significantly) more often among patients allocated to urokinase (3.6 vs 2.8%, p = NS). Congestive heart failure and pericarditis occurred significantly less often in patients receiving urokinase.

Adverse in-hospital clinical events (Table VII): Only 4 patients in the heparin group and 5 patients in the urokinase group were reported to have major bleeding

TABLE III Concomitant Cardiovascular Drugs During Hospitalization

	Groups	
	Control (n = 1,073)	Urokinase (n = 1,128)
Nitrates (%)	908 (84.72)	939 (83.33)
Calcium antagonists (%)	529 (49.39)	540 (47.96)
β blockers (%)	99 (9.23)	109 (9.75)
Antiarrhythmics (%)	340 (31.69)	408 (36.17)
Digoxin (%)	153 (14.35)	144 (12.77)
Diuretics (%)	287 (26.75)	255 (22.61)
Platelets antiaggregants (%)	288 (26.84)	353 (31.38)
Oral anticoagulants (%)	406 (37.93)	421 (37.32)
Subcutaneous heparin (%)	175 (16.31)	156 (13.83)

TABLE IV Overall Mortality and Causes of Death

	Urokinase (n = 1,128)	Control (n = 1,073)	RR (95% CI)	Total
Mortality (%)	7.97%	8.29%	0.96	8.13%
Deaths/no. of pts.	90/1,123	89/1,073	(0.70–1.31)	179/2,201
Causes of death				
Cardiac	85	85		170
Noncardiac	4	2		6
Undefined	1	2		3

CI = confidence interval; RR = relative risk.

(defined as a need for transfusion of >2 U of blood) (0.37 vs 0.44%, respectively, p = NS).

Minor bleeding (e.g., localized hematoma, ooze from puncture sites, hematuria, epistaxis or hemoptysis) were occurred more often in patients treated with urokinase than in control subjects (3.1 vs 1.3%, respectively, p = 0.07).

The overall stroke rate was very low (<0.5%) and comparable in the urokinase and heparin groups (0.35 vs 0.19%, respectively, p = NS); no differences were noted between the 2 treatments with regard to hemorrhagic and ischemic strokes. No differences were seen with respect to major postinfarction in-hospital rhythm disturbances (Table VIII).

DISCUSSION

The major finding of this trial was that no significant reduction in mortality was observed in patients with acute myocardial infarction treated with intravenous urokinase with anticoagulation therapy compared with patients treated with anticoagulation alone. Mortality was lower than expected in our heparin control group, only 8.3% compared with 13.0% in the GISSI-I⁹ and 13.2% in the Second International Study of Infarct Survival (ISIS-2) trial.¹¹ Overall mortality in this study is similar to that observed in GISSI-II.²⁰ It is obviously much more difficult for an intervention to improve survival in a setting in which the mortality rate in

TABLE V Mortality by Hours from Onset of Symptoms, Age, Site and Type of Acute Myocardial Infarction

	Urokinase (n = 1,128)	Control (n = 1,073)	p Value	RR (95% CI)	Total
Hours					
≤ 2	7.05% (45/596)	7.81% (42/538)	NS	0.96 (0.56–1.43)	7.76% (88/1,134)
> 2	9.02% (48/532)	8.79% (47/535)	NS	1.03 (0.66–1.60)	8.90% (95–1,067)
Age (years)					
≤ 70	5.90% (54/916)	5.81% (50/860)	NS	1.01 (0.67–1.54)	5.29% (94/1,776)
> 70	16.98% (36/212)	18.31% (39/213)	NS	0.91 (0.54–1.55)	17.60% (75/425)
Site and type of AMI					
Anterior	10.48% (52/496)	13.90% (61/439)	NS	0.73 (0.48–1.10)	12.10% (113/935)
Inferior	5.81% (32/541)	3.20% (16/500)	0.04	1.87 (0.99–3.67)	4.61% (48/1,041)
Non-Q-wave	6.59% (6/91)	8.96% (12/134)	NS	0.75 (0.23–2.16)	8.00% (18/225)

AMI = acute myocardial infarction; CI = confidence interval; NS = not significant; RR = relative risk.

TABLE VI Nonfatal Cardiac Events

	Urokinase (n = 1,128)	Control (n = 1,073)	p Value	Total
Nonfatal reinfarction	3.60% (41)	2.80% (30)	NS	3.20% (71)
Recurrent ischemia	14.00% (158)	15.40% (165)	NS	14.70% (323)
Overall ischemic events	17.60% (199)	18.20% (195)	NS	17.80% (394)
Other cardiac events				
Congestive heart failure	5.76%	9.88%	0.0004	
Pericarditis	4.88%	7.55%	0.0012	

NS = not significant.

TABLE VII Adverse In-Hospital Clinical Events

	Urokinase (n = 1,128)	Control (n = 1,073)	p Value	Total
Stroke (no. of pts.)	4 (0.35%)	2 (0.19%)	NS	6 (0.27%)
Ischemic	1	1		
Hemorrhagic	2	1		
Undefined	1	—		
Total bleeding (no. of pts.)	40 (3.55%)	18 (1.67%)	0.05	58 (2.63%)
Major	5 (0.44%)	4 (0.37%)	NS	
Minor	35 (3.10%)	14 (1.30%)	0.07	
Pulmonary and systemic thromboembolism (no. of pts.)	9 (0.80%)	7 (0.65%)	NS	

NS = not significant.

the control patients is low. The reasons for this finding are unclear. The selection of patients may have had some role, although the protocol did not exclude high-risk patients (e.g., those in cardiogenic shock) and elderly patients. At the time of randomization, pulmonary edema was more frequent in the urokinase group than in the heparin group, although the number of patients with such a complication was low in both groups. However, this does not completely explain the lack of difference in mortality rate between the 2 treatment groups since several anecdotal reports suggest that early reperfusion in such patients occasionally may exert a salutary effect.²¹ Finally, early treatment with intravenous heparin may have affected the outcome. The role of early intravenous heparin as monotherapy in acute myocardial infarction has not been established. Because heparin may have a complementary independent benefit,^{4,22–24} one cannot exclude the fact that heparin alone may lower mortality rate in acute myocardial infarction, as shown for aspirin in the ISIS-2 trial.¹¹ Prospec-

tive and randomized studies are needed with this regard.

A second major finding of this trial was the significant reduction of heart failure and pericarditis in the urokinase group compared with the control arm. Although assessment of ventricular function and infarct size was not attempted, this finding suggests that patients taking urokinase had smaller infarcts and better

TABLE VIII Postinfarction In-Hospital Rhythm Disturbances

	Urokinase (n = 1,128)	Control (n = 1,073)	p Value	Total
Ventricular fibrillation	33 (2.90%)	22 (2.05%)	NS	55 (2.50%)
Sustained VT	74 (6.60%)	84 (7.80%)	NS	158 (7.20%)
Complete heart block	20 (1.80%)	28 (2.60%)	NS	48

NS = not significant; VT = ventricular tachycardia.

left ventricular function probably as a result of an earlier reperfusion with myocardial salvage.

Finally the 2 treatments appeared to be equally safe in terms of major bleeding and overall incidence of stroke.

Subgroup analysis: Mortality tended to be lower among patients with anterior infarctions who received urokinase. Analysis of the relative risk demonstrated that urokinase reduced mortality in anterior infarction by about 27%, although the difference did not reach statistical significance. These findings are comparable with those obtained in other larger trials (GISSI I⁹ and ISIS-2¹¹).

Currently, we can offer no explanation for the apparent harmfulness of urokinase in the subset of patients with inferior wall infarcts. However, it should be emphasized that reliable identifications of subgroups of patients among whom treatment is particularly advantageous (or among whom it is ineffective or even harmful) is unlikely in a relative small sample-sized trial as this.¹¹ A trend toward a higher mortality in particular subgroups treated with thrombolysis has been observed also in larger trials, such as GISSI⁹ (e.g., patients with lateral infarcts or ST depression). On the other hand, one must consider that, when corrected for infarct size, the extent of left ventricular dysfunction caused by inferior wall infarction is about half of that produced by anterior wall infarction,²¹ and the prognosis for both short- and long-term survival is usually excellent. Therefore, the potential risks of thrombolytic therapy (including reperfusion injury) probably outweigh the benefits in patients with a small inferior wall infarct.

Study limitations: Several potential limitations of this study should be acknowledged. First, the lack of benefit of urokinase therapy shown in the study requires cautious interpretation due to the inadequacy of sample size. In fact, although this trial is certainly a large scale trial, it might not be large enough to detect mortality reduction, especially with the lower than anticipated control group mortality. Moreover, the relatively large number of patients excluded from the data analysis (patients with unconfirmed infarction and patients who did not have a discharge form), although equally distributed, might have further obscured possible differences between treatment groups.

Second, the admission to the study of patients with ST-segment depression at initial presentation may have affected the characteristics of the study population. In particular, the population with non-Q-wave infarction is too small to analyze separately, yet is large enough to detract from the main focus of the study.

Finally, our observations and conclusions must be limited to the dose of urokinase used. Although larger

doses yield similar rates of infarct vessel patency, a pronounced benefit from larger doses of urokinase therapy may yet be demonstrated.

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APPENDIX

Participating clinical centers: Agrigento "S.G.di Dio" (L. Nastri, R. Terrazzino, I. Vaccaro); Alba (G. Loparco, GL. Vigino, G. Galeazzo); Alghero (M. Spaned-da, M. Pittalis); Ancona "Lancisi" (N. Ciampiani, C. Costantini, G. Pigini); Arienzo (V. Zucconelli, A. Iervoglino, L. Piscitelli); Asti (CA. Caratti, G. Zola, A. Zanelli); Bari "Policlinico" (L. Colonna, C. D'Agostino, F. Bovenzi); Benevento (S. Lombardi, T. Messori, V. Moscato); Bologna "S. Orsola" (T. Lenzi, G. Trisolino, M. Cavazza); Borgosesia (M. Gronda, I. Contraffatto, R. Negro); Breno (G. Straneo, F. Glisenti); Caltagirone (G. Centamore, R. Di Caro, D. Malfitano); Camposampietro (M. Camponeschi, D. Corrado, A. Pantaleoni); Casarano (G. Pettinati, S. Monsellato, M. Ieva); Castrovillari (L. Vigna, G. Musca, C. Calvelli); Cavalese (G. Piazza, V. Moser, F. Barretta); Chivanna (A. Marolda, A. Tiberi); Civitanova Marche (F.

Greco, G. Traisci, T. Stacchiola); Colleferro (S. Sonnino, M. Mariani, M. Pagliei); Crotone (G. Zampaglione, F. Docimo, M. Elia); Cuneo (C. Bruna, A. Deorsola, N. De Benedictis); Domodossola (G. Tirella, M. D'Aulerio, G. Sauro); Firenze "S. Giovanni di Dio" (G. Zarbo, P. Innocente, G. Calculto); Firenze "Careggi" (PF. Fazzini, GM. Santoro); Fivizzano (LA De Giorgio, G. Pellegrini, PC. Rossi); Foligno (L. Tini Brunozzi, P. Paolucci, L. Meniconi); Fossombrone (G. Possanzini); Frascati (G. Giorgi, G. Pajes, L. Pandolfo); Galatina (R. Piazzalunga, R. Renna, G. Sticchi); Grosseto "Mise-ricordia" (N. Svetoni, A. Cresti, T. Lanzetta); La Spezia (G. Ragazzini, D. Bernabo', S. Battistini); Legnano (F. Passoni, F. Cafiero, M. D'Urbano); Livorno "Riuni-ti" (P. Del Bene, U. Baldini, A. Bertelli); Melito Porto Salvo (F. Ferraro, A. Romeo, A. Nucera); Merano (G. Salvato, M. Innerhofer, V. Pascarella); Messina "Piemonte" (G. Casella, F. Freni, U. Bitto); Messina "Policlinico" (F. Consolo, F. Arrigo, G. Oreto); Modica (G. Polara); Monfalcone (M. Palmieri, MT. Della Mea, P. Moratti); Montebelluna (R. Sandri, GF. Neri, R. Zampogna); Napoli "Cardarelli" (A. Cuomo, C. Cutino, O. Silvestri); Napoli "Vecchio Pellegrini" (A. Variale, A. Liguori, N. Di Ieso); Napoli "Ascalesi" (R. Santamaria, G. Granato Corigliano, A. Ruta); Nicosia (G. Bonarrigo, M. Fisicaro, C. Cacia); Nola (F. Napolitano, U. Pollice, G. Di Lorenzo); Ozieri (M. Sechi, C. D'Elia); Palermo "Civico" (V. Siragusa, A. Carrubba, L. Lo Presti); Perugia (P. Solinas, G. Bardelli); Piedimonte Matese (A. Cioffi, F. Vitale, G. Di Tommaso); Potenza (A. Rizzo, G. Paterno'); Reggio Calabria "Morelli" (E. Adornato, P. Monea); Rieti (A. De Sanctis, A. Mene'); Rivoli (C. Corradi, G. Barazia, G. Franco Loiri); Roma "S. Filippo Neri" (G. Altamura, S. Toscano, F. Lo Bianco); Roma "S. Giacomo" (V. D'Aiutolo, MS. Mennini, A. D'Egidio); Roma "S. Pietro" (F. Ferri, S. Capurso, PL. Delle Grotti); Roma "Umberto I" (MC. Borgia, A. Pasquale, C. De Martinis); Salerno "Da Procida" (U. Bugatti, A. Gigantino, G. Monaca); Saluzzo (G. Mauro, P. Allemano, G. Comba); San Benedetto del Tronto (B. Floris, M. Persico); Sassari "S. Annunziata" (G. Ibba, GM. Contini, M. Castellaccio); Savona "S. Paolo" (I. Filice, A. Gandolfo, GC. Torello); Sciaccia (F. Di Giovanna, G. Caramanno); Taranto "SS. Annunziata" (C. Montervino, G. Polimeni, V. Lenti); Tempio Pausania (L. Addis, PL. Bellu, GD. Filigheddu); Torremaggiore (RM. Piancone, MR. Rispoli, AM. Matarese); Velletri (MA. Ceccon, M. Rotondi); Venezia "Giustinian" (G. Gualandi, G. Sartore, G. Caturelli); Vercelli "S. Andrea" (M. Falcone, G. Cossa, C. Gabasio); Viareggio Pietrasanta (A. Pesola, G. Magini, C. Svetlich); and Vibo Valentia (V. Rosano, C. Bianco, VC. Colistra).

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Prediction of Major Cardiac Events After Peripheral Vascular Surgery Using Dipyridamole Echocardiography

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Patients undergoing peripheral vascular surgery are at increased risk of postoperative cardiac complications. To evaluate the role of dipyridamole echocardiography in predicting major cardiac events, 109 unselected patients undergoing elective peripheral vascular surgery were prospectively studied. Preoperative dipyridamole echocardiograms were interpreted by an echocardiographer unaware of all clinical data. Patients were followed up until hospital discharge by research physicians without knowledge of dipyridamole echocardiography results. Outcomes were classified using strict predefined criteria by reviewers unaware of other clinical and echocardiographic data. Of the 109 patients, 9 (8%) had positive studies defined as development of new regional wall motion abnormalities or worsening of preexistent wall motion abnormalities. Of these 9 patients, 7 had postoperative events, including 3 cardiac deaths, 1 nonfatal myocardial infarction, 2 with unstable angina, and 1 with pulmonary edema. Only 1 event occurred among the 100 patients with negative studies. The sensitivity and specificity of dipyridamole echocardiography for predicting cardiac events after vascular surgery were 88 and 98%, respectively; the positive and negative predictive values were 78 and 99%. The relative risk of having a cardiac event if dipyridamole echocardiography was abnormal was 78 (95% confidence interval, 11

to 564; $p < 0.0001$). If these results are extended and confirmed by other investigators, preoperative dipyridamole echocardiography may be an important screening test for patients undergoing elective peripheral vascular surgery.

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Patients undergoing peripheral vascular surgery are at increased risk for postoperative complications.¹⁻⁴ Preoperative assessment of cardiovascular risk is difficult in these patients because of the high frequency of conditions that preclude conventional exercise testing. Specialized preoperative tests such as dipyridamole thallium scintigraphy³⁻⁶ and ambulatory electrocardiographic monitoring^{2,7} have been highly sensitive in predicting perioperative cardiac events. However, because of the relatively low specificity and positive predictive value of these tests, a significant number of patients may have positive test results and not have a postoperative event. Such patients may be referred for unnecessary invasive testing and revascularization procedures, which may carry high risks because of coexistent vascular and renal disease. In a population with a relatively low predicted event rate, a screening test should have, in addition to high sensitivity, sufficient specificity and positive predictive value to minimize the number of false-positive studies. Dipyridamole echocardiography has been reported to be a highly specific test for detecting coronary artery disease.⁸⁻¹³ The aim of this study was to test the hypothesis that dipyridamole echocardiography, by virtue of its high specificity for coronary artery disease, is an independent predictor of perioperative cardiac events in patients undergoing noncardiac vascular surgery.

METHODS

Patient population: One hundred thirty-one patients scheduled to have vascular operations — excluding thoracic, venous and emergency procedures — from September 1989 to July 1990 were prospectively screened. Fifteen patients could not be enrolled because dipyrida-

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TABLE 1 Clinical Correlates of Postoperative Events

Correlate	Event Occurred (n = 8)	No Event (n = 101, 93%)	p Value
Age (mean \pm SD)	69 \pm 8	67 \pm 9	NS
Men/women	5/3	61/40	NS
Surgery			
Aortic	1	35 (32%)	NS
Femoral	4	42 (39%)	NS
Carotid	1	10 (9%)	NS
Other	2	14 (13%)	NS
β blocker	3	31 (28%)	NS
Calcium antagonist	3	29 (27%)	NS
Past smoking	2	49 (45%)	NS
Present smoking	4	37 (34%)	NS
Systemic hypertension	6	64 (59%)	NS
Diabetes mellitus	5	27 (25%)	≤ 0.05
Angina pectoris	2	12 (11%)	NS
Congestive heart failure	0	16 (15%)	NS
History of myocardial infarction	5	32 (29%)	NS
History of CABG or PTCA	2	16 (15%)	NS
Rales	1	8 (7%)	NS
S3 gallop	0	2 (2%)	NS
Abnormal ECG	7	67 (62%)	NS
Q wave on ECG	4	70 (64%)	NS

Except for age, all variables expressed as absolute number (percent of total). CABG = coronary artery bypass graft; ECG = electrocardiogram; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

mole was not available at the time of the scheduled operation. The protocol excluded patients with angina at rest ($n = 2$), myocardial infarction within 2 weeks of screening and failure to give informed consent ($n = 5$). The remaining 109 patients comprised the study group. Each patient had a detailed history and physical examination by research physicians. Each patient was independently evaluated preoperatively by a staff cardiologist who judged the surgical risk to be acceptable. Caffeine and theophylline preparations were withheld for a minimum of 24 hours before testing.

Dipyridamole echocardiograms: All patients had baseline 2-dimensional echocardiograms immediately after peripheral angiography. Dipyridamole was infused intravenously through an antecubital catheter at a rate of 0.14 mg/kg/min for 4 minutes with continuous blood pressure and electrocardiographic monitoring. Six minutes after the beginning of the infusion, a repeat 2-dimensional echocardiogram was recorded. If the patient remained asymptomatic and there was no evidence of ischemia, an additional 0.14 mg/kg/min of dipyridamole was infused for 2 minutes, bringing the total dose to 0.84 mg/kg. At this time, a third 2-dimensional echocardiogram was recorded. Two-dimensional echocardiograms were recorded with a Hewlett-Packard 77020 AC/AR phased-array ultrasonoscope device using a 2.5-MHz transducer. Images were obtained from the parasternal short-axis, parasternal long-axis, apical 2-chamber and apical 4-chamber views. In cases in which parasternal short-axis images were not ade-

quate, short-axis images were obtained from the subcostal view.

All echocardiograms were evaluated preoperatively by a single echocardiographer unaware of the clinical and electrocardiographic responses to dipyridamole and all other clinical information. All echocardiograms were then analyzed postoperatively by a second blinded echocardiographer in order to examine interobserver variability. In keeping with current recommendations,¹⁴ each echocardiographer had previous experience interpreting >100 stress echocardiographic studies. Systolic ventricular function was qualitatively graded as normal, mildly reduced, moderately reduced, or severely reduced. The presence of left ventricular hypertrophy was assessed from the 2-dimensional echocardiogram using American Society of Echocardiography standards.¹⁵ Left ventricular segmental anatomy was identified using standard nomenclature.¹⁶ Segments were scored for qualitative segmental wall motion (0 = normal; 1 = hypokinesia; 2 = akinesia; 3 = dyskinesia). Studies were classified as positive based only on the development of (1) a new transient regional wall motion abnormality in a region normal at rest; or (2) marked worsening of a previous regional dyssynergy by either an increase in severity (hypokinesia to dyskinesia) or extension of a baseline abnormality to adjacent segments.^{13,17-19} The clinical and electrocardiographic response to dipyridamole was recorded but was not a factor in determining test positivity. Minor worsening of a previous regional dyssynergy (hypokinesia to akinesia or akinesia to dyskinesia) or equivocal degrees of hypokinesia were not recorded.

Postoperative follow-up: After surgery, patients were followed until hospital discharge by research physicians unaware of echocardiographic results. Patients underwent 12-lead electrocardiography before their operations and on postoperative days 1 through 3. Serum creatine kinase levels were measured with MB fractionation²⁰ every 8 to 12 hours on postoperative days 1 and 2. Classification of postoperative events was performed using strict predefined criteria by an independent physician unaware of other clinical and echocardiographic data. Cardiac events were defined as: death from cardiac causes; nonfatal myocardial infarction (new Q waves >0.03 second, or creatine kinase >2.7 μ mol/s/liter with MB >5%); unstable angina (characteristic chest pain and ≥ 1 mm of ST-segment depression in ≥ 2 leads); or pulmonary edema confirmed by chest radiographic findings. For unstable angina and pulmonary edema, management in an intensive care unit or a change in medication was required.

Statistical analysis: In the univariate analysis, associations between major cardiac events and possible clinical and test predictors were examined using the chi-

TABLE II Clinical Response to Dipyridamole

	Tests		p Value
	Positive (n = 9, 8%)	Negative (n = 100, 92%)	
Mean increase in heart rate (beats/min)	12 ± 6	13 ± 8	NS
Mean decrease in systolic blood pressure (mm Hg)	17 ± 7	17 ± 9	NS
Chest pain	3	3 (3.0%)	≤ 0.05
ST depression	6	3 (3.0%)	≤ 0.01
Aminophylline administered	9/9	12/100	NS

Chest pain and ST depression expressed as absolute number (% of column).
NS = not significant.

square test with appropriate degrees of freedom for categorical variables and the Student's *t* test for continuous variables. The clinical variables considered are listed in Table I. Variables from dipyridamole echocardiography included the presence of systolic left ventricular dysfunction, baseline regional wall motion abnormalities, development of chest pain, or ≥1 mm of ST depressions after dipyridamole infusion, and the parameter of interest, inducible regional wall motion abnormalities. The relative risk of an event was assessed for patients with or without positive results on dipyridamole echocardiograms and compared by chi-square statistic (all *p* values are 2-tailed). A kappa statistic was calculated to assess the statistical significance of interobserver agreement.

RESULTS

Patient characteristics (Table I): Patients were aged 67.6 ± 8.9 years (mean ± standard deviation) and 66 (61%) were men. Ninety-two patients (84%) reported past or current cigarette use, 32 (29%) were diabetic, and 70 (64%) had a history of hypertension. Thirty-seven patients (34%) had a history of myocardial infarction and 18 (17%) had had percutaneous transluminal coronary angioplasty or coronary artery bypass surgery. Thirty-four patients (31%) were taking a β blocker and 32 (29%) were taking a calcium antagonist at the time of operation. There were 36 (33%) abdominal aortic procedures, 46 (42%) femoral artery procedures, 11 (10%) carotid endarterectomies and 16 (15%) other vascular procedures.

Dipyridamole echocardiograms: Adequate acoustic windows were obtained in all patients. Interobserver reproducibility for interpretation of dipyridamole echocardiograms was excellent, with agreement as to the presence or absence of significant new regional wall motion abnormalities in 108 of 109 studies (99%; kappa statistic = 0.94). The only disagreement occurred on a study that was interpreted as negative by the primary reader and positive by the secondary reader. The index subject had an uneventful postoperative course.

TABLE III Dipyridamole Echocardiographic Correlates of Postoperative Events

ECG Variables	Event		p Value
	Occurred (n = 8)	No Event (n = 101, 93%)	
Left ventricular hypertrophy	5	55 (54.5%)	NS
Left ventricular dysfunction	3	19 (18.8%)	NS
Resting regional wall motion abnormality	6	36 (35.6%)	≤ 0.05
Inducible regional wall motion abnormality	7	2 (2.0%)	≤ 0.0001
Dipyridamole responses			
Chest pain	2	4 (4.0%)	≤ 0.05
ST depression	3	9 (8.9%)	≤ 0.01

All variables expressed as absolute number (% of column).
ECG = echocardiographic; NS = not significant.

Regional wall motion abnormalities were evident on the baseline 2-dimensional examination of 42 patients, 6 of whom had cardiac events (*p* < 0.05). Baseline left ventricular systolic function was normal in 87 patients, mildly reduced in 8, moderately reduced in 7 and severely reduced in 14. Of the 8 patients with postoperative cardiac events, 5 had normal systolic function and 1 had mild and 2 had moderately reduced function (*p* = not significant).

Dipyridamole echocardiography was abnormal in 9 patients, in each case only after the second dosing interval. Six patients (5.5%) complained of chest pain during dipyridamole infusion, 3 of whom had dipyridamole-induced wall motion abnormalities (Table II). Nine patients (8.3%) had ST depressions of ≥1 mm in 1 or more leads during dipyridamole infusion; 6 of these patients had dipyridamole-induced wall motion abnormalities. Patients experienced an average increase in heart rate of 13 ± 8 beats/min and an average decrease in systolic blood pressure of 17 ± 9 mm Hg (Table II). Twenty-one patients received intravenous aminophylline, 12 because of noncardiac side effects and 9 because of evidence of myocardial ischemia.

Postoperative cardiac events: Postoperative events occurred in 8 patients. Seven of 8 cardiac events occurred within 48 hours of surgery; 1 event occurred 77 hours after surgery. There were 3 cardiac deaths, 1 nonfatal myocardial infarction, 3 cases of unstable angina, and 1 case of pulmonary edema. Of the clinical variables examined (Table I), only diabetes had a statistically significant association with the occurrence of postoperative cardiac events (*p* < 0.05) although, because some of these variables were infrequent and the total number of events was small, this study lacked sufficient power to detect associations that might exist.

Correlation of dipyridamole echocardiography with postoperative cardiac events: Postoperative cardiac events were found more often in patients with abnormal dipyridamole echocardiograms (*p* < 0.0001), chest

pain during dipyridamole infusion ($p < 0.05$), ST depression during dipyridamole infusion ($p < 0.01$), and presence of regional wall motion abnormalities on the 2-dimensional echocardiogram at rest ($p < 0.05$) (Table III). The presence of echocardiographic evidence of left ventricular hypertrophy or global left ventricular dysfunction did not correlate with the occurrence of postoperative cardiac events.

Of the 9 patients who had positive dipyridamole echocardiograms, 7 (78%) had postoperative events, compared with 1 of the 100 patients with negative test results (relative risk, 78; 95% confidence interval, 11 to 564). The single patient with a negative dipyridamole echocardiogram who developed unstable angina during the postoperative period was receiving atenolol at the time of the study and had a baseline echocardiogram that revealed left ventricular dysfunction and multiple regional wall motion abnormalities at rest, making classification of the test difficult with criteria used in this study. The 2 patients with positive dipyridamole echocardiograms who did not have cardiac events had both prior myocardial infarctions and left ventricular dysfunction.

DISCUSSION

Noninvasive risk stratification of patients preparing to undergo noncardiac vascular surgery remains one of the most challenging problems facing cardiologists because of the high prevalence of concurrent coronary artery disease.¹ Several methods for estimating perioperative risk have been reported, many of which have been used in studying patients referred for testing, perhaps because of a suspected high risk for cardiac events.²¹⁻²³ Recently, Raby et al.² reported the high negative predictive value (99%) of preoperative ambulatory monitoring of ischemia in 176 patients who were not preselected because of a high likelihood of coronary artery disease or because they were referred for testing. However, the positive predictive value of ambulatory monitoring of ischemia for predicting major cardiac events was only 38%. In a study of 200 patients referred for dipyridamole thallium scintigraphy before vascular surgery, Eagle et al.³ reported a positive predictive value of 30% when thallium variables alone were used; this increased to 43% when clinical variables were included. Because of the low positive predictive value, it is possible that patients who are at low risk for postoperative cardiac events may be subjected to unnecessary invasive testing or have needed surgery delayed.

We prospectively studied 109 patients without preselecting those who had a high likelihood of coronary disease or who were referred for testing. Patients were studied while receiving stable medical regimens including β blockers and calcium antagonists. Under these conditions, we found a low incidence of death (3 of 109;

2.8%) and a relatively low risk of serious cardiac events (8 of 109; 7.3%). These rates are similar to those previously reported in several large series.^{1,2,4} Preoperative dipyridamole echocardiography was both sensitive (88%) and specific (98%). Several other test variables were also found to have statistically significant correlations with the occurrence of postoperative cardiac events, including baseline regional wall motion abnormalities ($p < 0.05$), development of ST depressions during dipyridamole infusion ($p < 0.01$), and development of chest pain during dipyridamole infusion ($p < 0.05$); however, the positive predictive values of these variables for predicting major cardiac events were 14, 33, and 33%, respectively. Of the clinical variables included in the analysis, only diabetes had a correlation with occurrence of postoperative cardiac events.

There are limited data available directly comparing ambulatory monitoring of ischemia with other tests of perioperative risk. In a pilot study conducted at this institution, 42 patients underwent both dipyridamole echocardiography and ambulatory monitoring of ischemia before elective peripheral vascular surgery.²⁴ Twenty-four of these 42 patients were also enrolled in a separate study investigating the incidence and significance of preoperative, intraoperative and postoperative electrocardiographic myocardial ischemia (Raby et al, unpublished observations). The results of these preliminary studies suggest that dipyridamole echocardiography may have a higher positive predictive value for predicting major cardiac events than ambulatory monitoring of ischemia; however, a study with a larger sample size is necessary to confirm this hypothesis.

The positive predictive value with dipyridamole echocardiography of 78% is significantly higher than that reported for other currently available tests of inducible ischemia, such as dipyridamole thallium scintigraphy³ and ambulatory monitoring of ischemia.² In addition, the test can be performed in approximately 20 minutes and does not require a prolonged interval for serial imaging as is the case with thallium scintigraphy. However, high-dose dipyridamole produces adverse effects in a significant number of patients, whereas medical complications of ambulatory monitoring of ischemia have not been reported (Table II). If the results of the present study are confirmed by other investigators and the costs of the other various testing options are defined, it will then be possible to perform a more definitive cost-benefit analysis to determine the optimal sequence of testing.

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Impairment of Left Ventricular Function During Coronary Angioplastic Occlusion Evaluated with a Nonimaging Scintillation Probe

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Impairment of left ventricular function during controlled myocardial ischemia induced by coronary angioplasty has been reported from angiographic and echocardiographic studies. Ejection fraction, peak ejection, peak filling rates, and end-systolic and end-diastolic volumes were investigated before, during and after coronary occlusion on-line with a nonimaging scintillation probe. The study consisted of 18 patients (mean age 59 ± 10 years) with coronary artery stenosis of $>70\%$. During balloon inflation of 60 seconds' duration, coronary occlusion pressure was 31.6 ± 12 mm Hg. There was no significant change in heart rate. Delay between first and second dilatation was 109 ± 63 seconds. Ejection fraction decreased from 53 ± 16 to $40 \pm 12\%$ (first dilatation, $p < 0.01$) and to $39 \pm 14\%$ (second dilatation, $p < 0.01$) and recovered to $51 \pm 16\%$ 5 minutes after the second dilatation. Peak ejection rate was significantly reduced during the first and second balloon inflations. Peak filling rate decreased from 2.5 ± 0.8 to 2.0 ± 0.7 end-diastolic volume $\cdot s^{-1}$ (first dilatation, $p < 0.01$) and to 1.8 ± 0.7 end-diastolic volume $\cdot s^{-1}$ (second dilatation, $p < 0.01$) and remained reduced at 2.2 ± 0.7 end-diastolic volume $\cdot s^{-1}$ ($p =$ not significant) at 5 minutes after the second dilatation. End-systolic and end-diastolic volumes increased significantly during the first and second dilatations and returned to normal after dilatation.

It is concluded that short, controlled myocardial ischemia during coronary angioplasty leads to a decrease in systolic and diastolic left ventricular function. Sequential dilatations do not further decrease function if a sufficient interval is kept. (Am J Cardiol 1991;68:598-602)

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Coronary angioplasty, besides being a well-established therapeutic tool in coronary artery disease, provides an attractive setting to study the effects of acute reversible coronary occlusion in humans. Transient changes in left ventricular (LV) function during reversible myocardial ischemia have been demonstrated angiographically¹⁻³ and echocardiographically.⁴⁻⁷

Radionuclide ventriculography has been used in the evaluation of acute and chronic therapeutic interventions and also during changes induced by coronary angioplasty in patients with coronary artery disease.⁸⁻¹² However, standard radionuclide ventriculography has not been used in the evaluation of brief, transient changes in LV function because long data acquisition times are needed. Nonimaging scintillation detectors have been applied in interventional short-term data acquisition studies such as exercise testing, isometric handgrip, cold stress testing and atrial pacing.¹³⁻¹⁵

We report on the evaluation of systolic and diastolic changes in LV function during reversible coronary ischemia as monitored with a newly developed miniature cesium iodide detector.

METHODS

Patients: Eighteen men (mean age \pm standard deviation 59 ± 10 years) admitted for elective coronary angioplasty gave informed consent to undergo a radionuclide study during the procedure. Criteria for inclusion in the study were a reduction of $>70\%$ in luminal diameter in 1 of the 3 major coronary arteries with indication for coronary angioplasty, normal regional and global systolic LV function at biplane ventriculography, and the absence of angiographically visible collateral vessels. Coronary angioplasty was performed in the left anterior descending coronary artery in 6 patients, in the right coronary artery in 6 patients, and in the circumflex branch of the left coronary artery in 6 patients.

Coronary angioplasty: Coronary angioplasty was performed by the brachial or femoral approach using the long wire technique¹⁶ with balloon catheters of 2.5 to 3.5 mm in diameter. Precordial electrocardiographic leads (V_4 , V_5) were continuously monitored. In addition to the surface electrocardiogram, the intracoronary

electrocardiogram via the coronary angioplasty guide-wire was recorded as a highly sensitive means of detecting myocardial ischemia. Each balloon inflation lasted 60 seconds using inflation pressures of 6 to 10 atm. Two inflations were performed on each patient, with electrocardiographic and clinical recovery occurring between balloon inflations.

Monitoring of left ventricular function: The non-imaging nuclear probe (Cardioscint®, Oakfield Instruments, Oxon, United Kingdom) is a device for measuring cardiac function by recording precordial radiation from the left ventricle after blood pool labeling with technetium-99m pertechnetate. The single cesium iodide crystal scintillation detector is small enough to be attached to the patient's chest and obtains high resolution background-subtracted time-activity curves by electrocardiographic gating.^{13,17,18} Comprehensive validation data have recently been published by Broadhurst et al.¹⁸ Red cell labeling was performed with 555 to 740 MBq of technetium-99m pertechnetate. The probe was positioned in a left anterior oblique projection by direct visualization similar to the left anterior position used for routine gamma camera interventions delivering best septal projection. The cavity of the left ventricle was identified using a gamma camera¹⁸ and the angulation of the detector producing the optimum time-activity curve was determined. The background region was defined inferolateral of the left ventricle. The position of the probe was marked on the chest wall to facilitate repositioning. As the actual relation between detector count rate and actual LV volume is never known precisely, there is an uncertainty of the probe in determining absolute LV volume. However, the method is suitable for monitoring changes in LV volume and function during short-term studies. Equilibrium scintillation data gated to the electrocardiogram were acquired with acquisition intervals of 10 seconds. The cor-

TABLE I Patient Characteristics

	No. of Pts.	Age (yrs)	Occlusion Pressure (mm Hg)	Severity of Stenoses	
				Before Angioplasty (%)	After Angioplasty (%)
All pts.	18	59 ± 10	31 ± 10	84 ± 9	21 ± 17
LAD	6	59 ± 5	33 ± 15	87 ± 10	23 ± 18
Right	6	57 ± 12	30 ± 7	84 ± 9	17 ± 15
LC	6	59 ± 14	27 ± 1	85 ± 8	19 ± 19

LAD = left anterior descending coronary artery; LC = left circumflex coronary artery.

relation coefficient between gamma camera and probe detector measurements was determined in 27 patients as 0.87 ($y = 0.79x + 6.1$) for ejection fraction, 0.85 ($y = 0.7x + 0.7$) for peak ejection rate, 0.7 ($y = 0.5x + 0.9$) for peak filling rate, 0.8 ($y = 0.26x + 30.5$) for end-systolic volume and 0.58 ($y = 0.2x + 68$) for end-diastolic volume indexes. Intra- and interobserver variability for ejection fraction measurements with the cesium iodide detector was 0.91 and 0.92.

Data analysis: Data are presented as mean ± standard deviation. Changes in ejection fraction, peak filling rate, and end-systolic and end-diastolic volumes obtained by continuous recording were evaluated by analysis of variance. The Wilcoxon signed rank test was then used to compare preintervention data with values obtained during the first and second balloon inflations and 5 minutes after coronary angioplasty.

Correlation of gamma camera and cesium iodide probe measurements were analyzed by regression analysis for ejection fraction, peak ejection rate, peak filling rate, and end-systolic and end-diastolic volumes.

RESULTS

Percutaneous transluminal coronary angioplasty:

All patients underwent successful coronary angioplasty (Table I). Occlusion pressure was determined as $31 \pm$

FIGURE 1. Effect of temporary coronary occlusion (60 seconds' duration) on left ventricular ejection fraction (mean ± standard deviation). pre PTCA = values before percutaneous transluminal coronary angioplasty; PTCA 1 = first coronary occlusion of 60 seconds' duration; PTCA 2 = second coronary occlusion of 60 seconds' duration; post PTCA = 5 minutes after the second balloon dilatation.

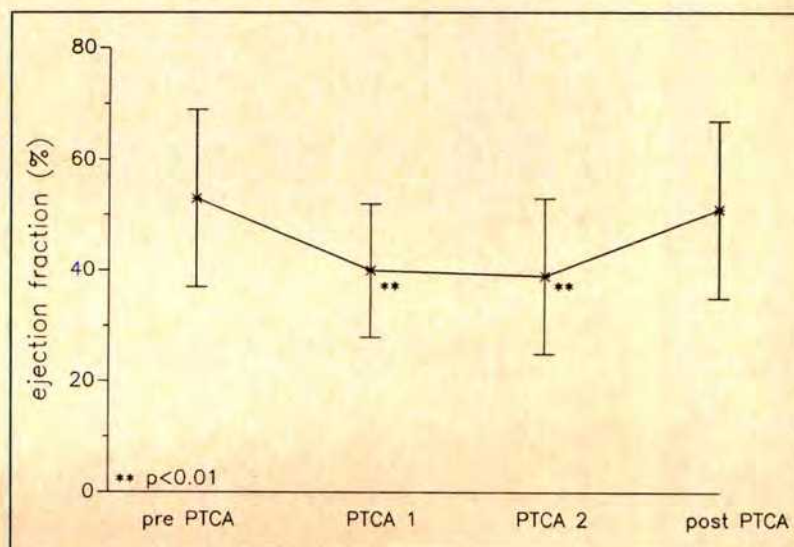


TABLE II Parameters of Systolic and Diastolic Function During Coronary Angioplasty in All Patients

Angioplasty	HR (min^{-1})	EF (%)	ESV	EDV	PER ($\text{EDV} \cdot \text{s}^{-1}$)	PFR ($\text{EDV} \cdot \text{s}^{-1}$)
Before	79 ± 15	53 ± 16	39 ± 28	70 ± 27	2.9 ± 0.9	2.5 ± 0.8
First dilation	30 ± 16	40* ± 12	50* ± 27	75* ± 26	2.3* ± 0.9	2.0* ± 0.7
Second dilation	79 ± 20	39* ± 14	53* ± 26	79* ± 25	2.2* ± 1	1.8* ± 0.7
After	77 ± 17	51 ± 15	42 ± 27	74 ± 26	2.7 ± 1	2.2 ± 0.7

* $p < 0.01$.
EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume;
HR = heart rate; PER = peak ejection rate; PFR = peak filling rate.

11 mm Hg. The second dilatation was performed 109 \pm 63 seconds after termination of the first balloon inflation. Each balloon inflation lasted 60 seconds. There were no statistically significant changes in heart rate.

Left ventricular systolic parameters: Ejection fraction was 53 \pm 16% before coronary angioplasty. It decreased significantly to 40 \pm 12 and 39 \pm 14% during the first and second balloon inflations ($p < 0.01$, Figure 1, Table II). Five minutes after the second coronary angioplasty, ejection fraction returned to preintervention values (51 \pm 15%). The index of end-systolic volume increased significantly, from 39 \pm 28 to 50 \pm 27 and 53 \pm 26 ($p < 0.01$) during inflations 1 and 2 and returned to preintervention values 5 minutes after dilatation (Figure 2, Table II). Peak ejection rate was significantly reduced during the first and second balloon inflations (from 2.9 \pm 0.9 to 2.3 \pm 0.9 and to 2.2 \pm 1 end-diastolic volumes $\cdot \text{s}^{-1}$, $p > 0.01$). Five minutes after coronary angioplasty it had not returned to normal (2.7 \pm 1 end-diastolic volume $\cdot \text{s}^{-1}$). The difference of peak ejection rate before and after angioplasty was statistically not significant (Table II).

Left ventricular diastolic parameters: End-diastolic volume increased significantly from 70 \pm 27 to 75 \pm 26

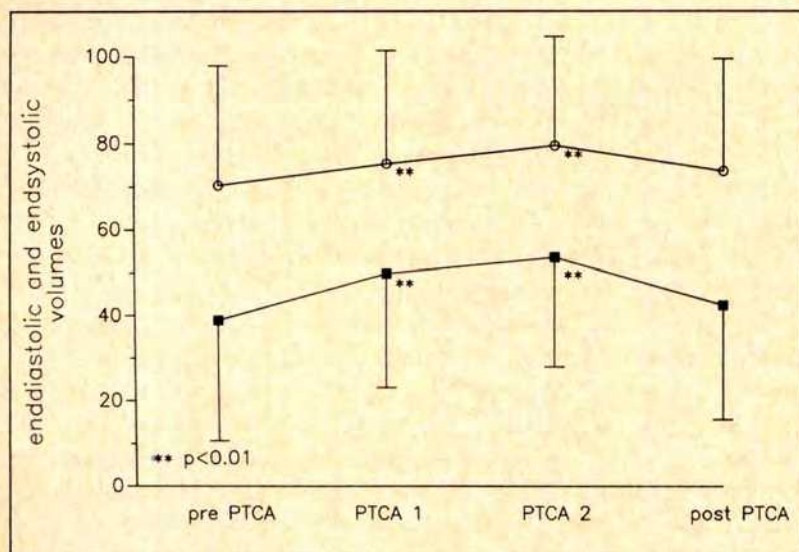


FIGURE 2. Effect of temporary coronary occlusion (60 seconds' duration) on left ventricular end-systolic (solid squares) and end-diastolic (open circles) volumes (mean \pm standard deviation). Abbreviations as in Figure 1.

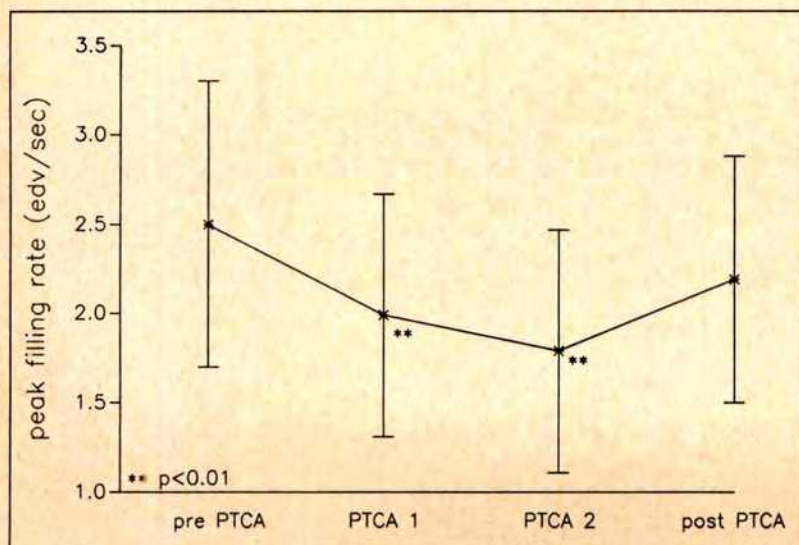


FIGURE 3. Effect of temporary coronary occlusion (60 seconds' duration) on left ventricular peak filling rate (mean \pm standard deviation). edv = end-diastolic volume; other abbreviations as in Figure 1.

during the first balloon inflation. During the second inflation, end-diastolic volume was still significantly increased at 79 ± 25 ($p < 0.01$). Five minutes after coronary angioplasty, the index of LV end-diastolic volume was still increased without reaching statistical significance (Figure 2, Table II). Peak filling rate was significantly reduced during the first and second balloon inflations (from 2.5 ± 0.8 to 2.0 ± 0.7 and to 1.8 ± 0.7 end-diastolic volumes $\cdot s^{-1}$, $p < 0.01$) and was still reduced 5 minutes after the last balloon inflation (Figure 3, Table II).

Impairment of left ventricular function during coronary angioplasty depending on the treated vessel: Ejection fraction decreased during angioplasty in all 3 major coronary vessels (Figure 4, Table III). In the left anterior descending coronary artery, ejection fraction decreased significantly from 57 ± 19 to $35 \pm 9\%$ and $35 \pm 10\%$ ($p < 0.05$) during the first and second balloon inflations and returned to $56 \pm 18\%$ 5 minutes after the second dilatation. Angioplasty of the circumflex branch led to a reduction in ejection fraction from 48 ± 17 to $39 \pm 16\%$ and to $40 \pm 19\%$ ($p < 0.05$) during the first and second balloon inflations and returned to $49 \pm 17\%$ 5 minutes after the second coronary occlusion.

Dilatation of the right coronary artery reduced ejection fraction from 54 ± 14 to $47 \pm 8\%$ and to $45 \pm 9\%$ ($p < 0.05$) and was still reduced 5 minutes after the second balloon inflation. However, this effect was not statistically different from preintervention values.

DISCUSSION

Reversible changes in LV function during coronary angioplasty have been demonstrated by angiographic and echocardiographic methods.^{3,5} Although ST-segment changes in the surface electrocardiogram have been the standard clinical marker for procedure-related ischemia, these changes generally occur after the onset

TABLE III Ejection Fraction (%) Before, During and After Coronary Angioplasty in Relation to the Treated Vessel

Angioplasty	LAD	LC	Right
Before	57 ± 19	48 ± 17	54 ± 14
First dilation	$35 \pm 9^*$	$39 \pm 16^*$	$47 \pm 8^*$
Second dilation	$35 \pm 10^*$	$40 \pm 19^*$	$45 \pm 9^*$
After	56 ± 18	49 ± 17	46 ± 12

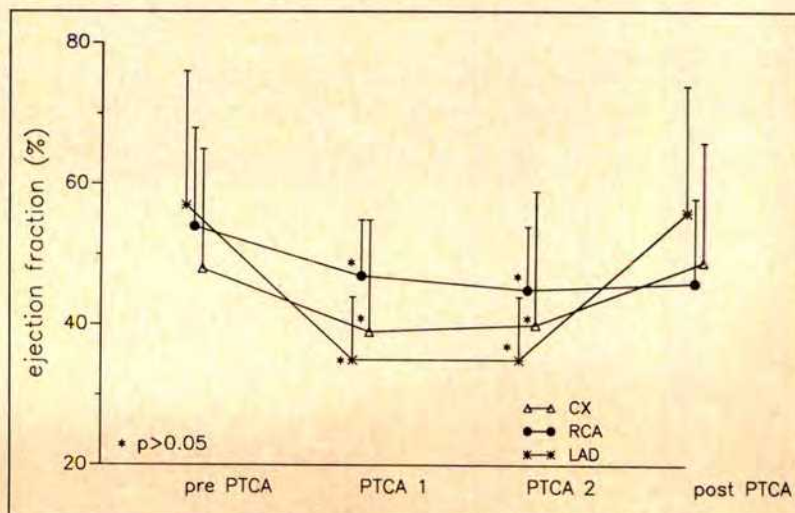
* $p < 0.05$.
Abbreviations as in Table I.

of contractile dysfunction and may not be evident in as many as 15% of patients who have impaired contractility.¹⁹ Nonimaging nuclear probes have been developed that are capable of evaluating LV function in the gated and beat-to-beat modes.²⁰ Further miniaturization of the probe now offers the chance of continuous LV function monitoring during interventional procedures in the cardiac catheterization laboratory.¹⁸

In this study, changes in LV systolic and diastolic function and relative changes in end-systolic and end-diastolic volumes during coronary occlusion could be demonstrated. In the angiographic study of Carlson et al,²¹ a 60-second balloon inflation reduced ejection fraction from 68 to 49% compared with a reduction from 53 to 40% found in this study. They selected an interval of 5 minutes between 2 balloon inflations and found no further reduction in ejection fraction during the second balloon inflation. Even with a much shorter interval of 109 seconds used between 2 balloon inflations, no further reduction in ejection fraction was seen in this study.

We found ejection fraction to be reduced more during occlusion of the left anterior descending coronary artery and the circumflex branch of the left coronary artery than during occlusion of the right coronary artery. This is in line with findings by Kass et al¹ who found systolic dysfunction characterized by a rightward shift of the end-systolic pressure-volume relation great-

FIGURE 4. Effect of temporary coronary occlusion (60 seconds' duration) of left anterior descending coronary artery (LAD), right coronary artery (RCA) and circumflex coronary artery (CX) on left ventricular ejection fraction (mean \pm standard deviation). Abbreviations as in Figure 1.



er for left anterior descending and circumflex coronary artery occlusion than for right coronary artery occlusion.

End-systolic volume increased by 26% during the first balloon occlusion. This is comparable to the data by Kass et al¹ who found a 43% increase in end-systolic volume on angiography during transient coronary occlusion combined with inferior vena cava occlusion. End-diastolic volume increased only by 7% during the first balloon occlusion. The study by Kass et al found little change in end-diastolic volume during temporary coronary occlusion and reported an invasively determined increase of 3%.

Changes in diastolic function have been reported during temporary coronary occlusion. Doppler-derived parameters revealed that early diastolic filling is compromised and late diastolic filling enhanced.⁴ Hemodynamic studies have shown a prolongation of the time constant of left ventricular pressure decay ($-dp/dt_{max}$) and an elevation of the diastolic pressure-volume relation^{1,21} during temporary coronary occlusion. With radionuclide angiography, as used in this study, a decrease in the peak filling rate of 21% during the first balloon inflation and of 29% during the second balloon inflation was observed, with recovery to predilatation values within 5 minutes after the second coronary occlusion. Whether impairment of diastolic function during temporary coronary occlusion is only due to changes in myocardial properties or also due to pericardial constraint has been a matter of debate.^{1,4,21}

This study demonstrates the efficacy of a miniaturized nonimaging scintillation detector in evaluating LV systolic and diastolic function during sequential balloon inflations during coronary angioplasty. Transient ischemia during coronary angioplasty leads to a decrease in systolic and diastolic LV function. Sequential dilations do not further decrease function if a sufficient interval is kept.

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Use of Amiodarone for Short-Term and Adjuvant Therapy in Young Patients

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Limited data are available defining the safety of amiodarone for short-term use or as part of combination antiarrhythmic therapy in pediatric patients. Results of amiodarone in 47 young patients for an average treatment duration of 12 months were examined. There were 21 male and 26 female patients (age range of 23 weeks gestation to 29 years). Patients were divided into 4 groups: group 1—electrocardiographic documented ventricular tachycardia ($n = 7$); group 2—syncope of unknown cause ($n = 16$); group 3—primary atrial tachycardia ($n = 11$); and group 4—supraventricular tachycardia ($n = 13$). Amiodarone was clinically useful in 32 (68%) patients. Amiodarone was considered effective as a sole antiarrhythmic agent in 21 (45%) patients. Treatment was ineffective but was continued in 11 (23%) patients; in 10 of these 11 patients amiodarone was adjuvant to other antiarrhythmic drugs. Amiodarone was considered ineffective and was withdrawn in 15 (32%) patients. No patient required cardiac pacemaker implant during therapy. Torsades de pointes and cardiac arrest occurred in 1 patient each after 9 and 14 days of therapy, respectively. Two patients underwent successful cardiac transplant after 2 and 14 months of amiodarone administration, respectively. Amiodarone was used as short-term treatment (<18 months) in 7 infants (age <18 months), and after cessation of treatment there was no recurrence of tachycardia for 4 to 24 months.

Results of this study confirm reports of successful amiodarone use in pediatric patients with a variety of rhythm disturbances. Results in the

pediatric patients evaluated in this study indicate that amiodarone is useful both as short-term treatment and as adjuvant therapy with other antiarrhythmic drugs.

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Amiodarone has been shown to be useful as a single antiarrhythmic drug in the management of a variety of rhythm disturbances in young subjects.¹⁻⁵ However, concerns about adverse effects that occur during long-term administration have limited the acceptance of amiodarone for use in young patients.⁶⁻⁸ Limited data are available defining the safety of amiodarone for short-term use or as part of combination antiarrhythmic therapy. The purpose of this report was to investigate the use of amiodarone in pediatric patients, emphasizing short-term treatment and adjuvant therapy.

METHODS

Patients: Amiodarone was used in 47 patients at the Children's Memorial Hospital, Chicago, Illinois, between July 1986 and December 1990. Indications for amiodarone administration were largely based on the judgment of the patient's physician, with particular consideration given to type of rhythm disturbance, severity of associated symptoms, clinical condition of the patient and previous antiarrhythmic drug trials.

Patient management: All 47 patients underwent transvenous or transesophageal electrophysiologic study in order to characterize the known or suspected rhythm disturbance before initiation of amiodarone.^{9,10} Protocol for oral amiodarone administration consisted of a loading dose of 10 to 20 mg/kg/day for 7 to 10 days, followed by a maintenance dose of 5 to 10 mg/kg/day. Early in the study, all patients were hospitalized for 1 to 2 days during the loading period, and continuous electrocardiographic monitoring was performed. However, during the past year, amiodarone therapy was begun on an outpatient basis in most patients. Ambulatory electrocardiographic monitoring was performed at the end of the loading period. During therapy with a

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TABLE I Group One, Electrocardiographic Documented Ventricular Tachycardia

Pt. No.	Heart Disease	Age (yr)	Symptoms	Type of VT	Previous Drugs	Amiodarone Duration (yr)	Outcome
1	Myocarditis	1.1	CHF	Incess.	3	1.4	IC*
2	WPW	1.2	Cardiac arrest	Mono.†	3	0.7‡	IC*
3	OC	1.4	CHF	Incess.	2§	1.3	IC*
4	O	9.3	Syncope	Poly.	3	0.1	IW
5	O	11	Cardiac arrest	Poly.	0	2.4‡	CE
6	DORV/AS	12	Palpitations Presyncope	Mono.	0	1.7‡	CE
7	TOF	16	Presyncope	Mono.	2	1.5	CE

*Additional therapy.
†ORT also present.
‡Presently on amiodarone.
§Digoxin.
AS = aortic stenosis; CE = considered effective; CHF = congestive heart failure; DORV = double outlet right ventricle; IC = ineffective, continued; Incess. = incessant; IW = ineffective, withdrawn; Mono. = monomorphic; OC = oncocytic cardiomyopathy; ORT = orthodromic reciprocating tachycardia; Poly. = polymorphic; TOF = tetralogy of Fallot; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome; O = no heart disease.

TABLE II Group Two, Syncope of Unknown Cause

Pt. No.	Heart Disease	Age (yr)	Arrhythmia	Drugs	Previous Duration (yr)	Amiodarone Outcome
1	O	3.0	Poly. VT,* CVE	1	0.2†	CE
2	Neonatal MI	7.3	Mono. VT,* CVE	1‡	3.2†	CE
3	O	9.2	Poly. VT,* CVE	2	0.8	IW
4	O	13	Poly. VT*	0	1.4	IW
5	DC	13	Poly. VT,* CVE	0	2.4	IW§
6	O	14	Poly. VT*	0	1.7	CE
7	O	14	Poly. VT,* CVE, AF	2	0.4	CE
8	O	14	Poly. VT*	0	0.3	IW
9	O	15	Poly. VT*	0	2.2	CE
10	O	15	Poly. VT*	0	2.9	IW
11	O	16	O	4	0.1	IW
12	O	17	Poly. VT*	0	0.5	IW
13	O	17	Poly. VT,* CVE	0	2.0	CE
14	O	18	AET	2‡	0.2	IW§
15	O	19	Poly. VT,* CVE	0	1.2	IW
16	d-TGA, VSD, PS	20	Poly. VT,* CVE, AVB	0‡	0.4†	CE

*Pacing induced.
†Presently on amiodarone.
‡Digoxin.
§Additional therapy.
AET = automatic ectopic atrial tachycardia; AF = atrial flutter/fibrillation; AVB = atrioventricular block; CE = considered effective; CVE = complex ventricular ectopy; DC = dilated cardiomyopathy; d-TGA = transposition of great arteries; IW = ineffective, withdrawn; MI = myocardial infarction; Mono. = monomorphic; Poly. = polymorphic; PS = pulmonary stenosis; VSD = ventricular septal defect; VT = ventricular tachycardia; O = no heart disease.

maintenance dose and for the first 6 months after discontinuation of therapy, symptoms were carefully monitored; ambulatory electrocardiographic monitoring was obtained every 3 or 6 months, as judged necessary by the patient's physician. Serum concentration of amiodarone and desethylamiodarone, and thyroid and liver function were assessed twice annually during treatment.

Assessing outcome: Amiodarone was considered ineffective and was withdrawn if there was a worsening or no improvement of symptoms, or a proarrhythmic action. Amiodarone was considered ineffective but its administration was continued when there was an evident lessening of symptoms and a subjective impression of improvement of tachycardia-free intervals in patients with non-life-threatening arrhythmias. Finally, amiodarone was considered effective when there was abolition of symptoms and arrhythmia during follow-up. At the discretion of the patient's cardiologist, amiodarone

was discontinued in most patients after an arrhythmia-free period (usually 8 to 10 months, but as short as 2 months).

Patient groups: The patients were divided into 4 groups: patients with electrocardiographic documented ventricular tachycardia (group 1); patients with syncope of unknown cause (group 2); patients with primary atrial tachycardia and history of cardiac surgery (group 3); and patients with supraventricular tachycardia who had no surgery (group 4).

Group 1 (documented ventricular tachycardia): Administration of amiodarone was begun in 7 patients (age range 1.1 to 16 years) (Table I). Sustained paroxysmal monomorphic ventricular tachycardia was documented in 3 patients; a previous history of cardiac arrest and associated Wolff-Parkinson-White syndrome was present in 1 of these patients. Incessant ventricular tachycardia was present in 2 patients and polymorphic

TABLE III Group Three, Primary Atrial Tachycardia, Postoperative

Pt. No.	Heart Disease	Age (yr)	Symptoms	Cycle Length	Previous Drugs	Amiodarone Duration (yr)	Outcome
1	I-TGA	0.7	CHF	210	1*	0.1†	CE
2	TAPVC, CAVC	1.2	Palpitations	250	0*	0.4†	CE
3	DORV	5.3	Palpitations	210‡	1*	0.2	IW
4	d-TGA	7.3	Palpitations	210‡	1*	0.2	IW
5	VSD	7.5	Palpitations, CHF	160‡	5*	0.2	IW
6	d-TGA, VSD	10	Palpitations	170‡	1*	0.2	IW
7	TOF	21	Palpitations	300	1*	0.1†	CE
8	d-TGA	21	Palpitations	260‡	2*	1.1	IW
9	TOF, ASD	23	Palpitations	420	6	1.8†	CE
10	DORV	25	Palpitations	320‡	2	1.6†	IC
11	TOF	29	Palpitations	320	3*	2.2†	CE

*Digoxin.

†Presently on amiodarone.

‡Sustained.

ASD = atrial septal defect; CAVC = complete atrioventricular canal; I-TGA = corrected transposition of great arteries with Ebstein's malformation; TAPVC = total anomalous pulmonary venous connection; other abbreviations as in Tables I and II.

TABLE IV Group Four, Supraventricular Tachycardia, Nonoperated

Pt. No.	Heart Disease	Age (yr)	Symptoms	Arrhythmia	Previous Drugs	Amiodarone Duration (yr)	Outcome
1	0	23 weeks	Hydrops	ORT	2*	0.1	CE
2	0	0.1	None	Chaotic AT	0*	0.2	CE
3	Scimitar	0.1	CHF	ORT, ART	2*	1.4	IC†
4	0	0.1	CHF	ORT, AF	1*	0.2‡	CE
5	0	0.2	CHF	ORT	2*	0.8	IC†
6	0	0.4	CHF	AET	0*	0.8	CE
7	0	0.5	CHF	PJRT	3*	0.5	IC†
8	0	3.1	CHF	PJRT	3*	1.6‡	CE
9	0	5.8	CHF	AET	1*	0.2‡	IC†
10	0	7.7	Palpitations	IART	2*	1.2‡	IC†
11	0	9.5	CHF	AET	1	2.0	IC†
12	0	10	Palpitations	JET	3*	1.6	CE
13	0	10	CHF	AET	0	0.2‡	IC†

*Digoxin.

†Additional therapy.

‡Presently on amiodarone.

ART = antidromic reciprocating tachycardia; AT = atrial tachycardia; Hydrops = hydrops fetalis; IART = intraatrial reentry tachycardia; JET = junctional ectopic tachycardia; PJRT = permanent form of junctional reciprocating tachycardia; Scimitar = scimitar syndrome; other abbreviations as in Tables I and II.

ventricular tachycardia was present in 2 patients, 1 of whom had cardiac arrest. Associated heart disease was present in 4 patients.

Group 2 (syncope of unknown cause): Sixteen patients had ≥ 3 syncope episodes of unknown cause. Age at onset of amiodarone therapy ranged from 3 to 20 years (Table II). No patient had electrocardiographic documentation during syncope, but complex ventricular ectopy was present in 8 patients, 3 of whom had other associated heart disease. In the remaining 13 patients, the heart was ostensibly normal. Most patients had polymorphic ventricular tachycardia induced during ventricular stimulation with 3 or 4 extrastimuli.

Group 3 (postoperative primary atrial tachycardia): Eleven patients had primary atrial tachycardia 0.1 to 15 years (mean 5.1) after heart surgery. Age at onset of amiodarone therapy ranged from 0.7 to 29 years (Table III). In 6 patients, the episodes of primary atrial tachycardia were sustained and each occurrence required cardioversion,¹¹ whereas in the remaining 5 pa-

tients the tachycardia episodes were frequent but spontaneously terminated in seconds to minutes.

Group 4 (supraventricular tachycardia): Thirteen patients had supraventricular tachycardia and no history of previous heart surgery. Age at onset of amiodarone treatment ranged from 23 weeks gestation (prenatal) to 10 years (Table IV). Patient 1 presented with hydrops fetalis and tachycardia with atrioventricular association; maternal therapy with amiodarone was instituted after having no success with digoxin and 2 additional antiarrhythmic drugs.

Statistical methods: The 4 groups were compared using the analysis of variance and the chi-square test, as appropriate, by way of the SPSS-PC+ statistical package.

RESULTS

Results were reported on 47 patients. There were 21 male and 26 female patients (age range of 23 weeks gestation [prenatal] to 29 years). Average duration of

TABLE V Adjuvant Therapy

Group	Pt No.	Arrhythmia	Combined Therapy	Duration (yr)
1	1	VT	β blocker and mexiletine	0.1
1	2	VT	β blocker and mexiletine	0.1
1	3	VT	β blocker and mexiletine	0.9
2	5	VT	β blocker	1.0
2	14	AET	β blocker	0.2
4	3	ORT, ART	Verapamil	0.1
4	5	ORT	Verapamil	0.7
4	7	PJRT	Verapamil and procainamide	0.5
4	9	AET	Verapamil	0.2
4	10	IART	Quinidine, disopyramide or procainamide	0.7
4	11	AET	Verapamil	2.0
4	13	AET	Verapamil, β blocker and procainamide	0.2

Abbreviations as in Tables I, II and IV.

amiodarone administration was 12 months (range 15 days to 2.9 years). Ages at onset of the rhythm disturbance and at onset of amiodarone therapy were lower in group 4 than in the other groups, but no difference was found in the total duration of amiodarone treatment among the groups. No significant differences in the outcome of therapy could be found among the groups.

As a single antiarrhythmic agent, amiodarone was considered effective in 21 (45%) patients. Amiodarone was considered ineffective but treatment was continued in 11 (23%) patients; in 10 of these patients, amiodarone was used in combination with additional antiarrhythmic drugs. Thus, amiodarone was clinically useful in 32 (68%) patients. Amiodarone was considered ineffective and was withdrawn in 15 (32%) patients.

Clinical use versus groups: Amiodarone was useful in treating 6 of 7 group 1 patients. In 3 of these patients amiodarone was considered effective, whereas in the remaining 3 it was ineffective alone, but was continued in combination with other antiarrhythmic drugs (Table V). Amiodarone was useful in group 2 patients with syncope of unknown cause when complex ventricular ectopy was present; in 5 of 8 such patients amiodarone was considered effective (Table II). Amiodarone was useful in 5 group 3 patients with frequent primary atrial tachycardia episodes that spontaneously terminated and did not require cardioversion. In all 5 such patients, the drug was considered effective (Table III). Amiodarone was most useful in the 13 group 4 patients with supraventricular tachycardia. Amiodarone was considered effective in 6 of these patients (Table IV). It was ineffective but continued with additional therapy in the 7 remaining patients (Table V). In no group 4 patient was amiodarone considered ineffective and withdrawn.

Presence of adverse effects: Six patients (12.5%) experienced proarrhythmia or adverse effects from amiodarone therapy. Patient 4 in group 1 developed tor-

sades de pointes after 9 days of amiodarone therapy, whereas patient 14 in group 2 had his first cardiac arrest with documented ventricular fibrillation after 14 days of amiodarone therapy. Both patients were resuscitated and the drug was discontinued. Patients 2 and 6 in group 2 developed photosensitivity. After reduction of sun exposure and the use of sunscreens, mild symptoms were well-tolerated in 1 patient, but drug withdrawal was required in another patient. Patient 10 in group 4 developed adverse effects while taking amiodarone in combination with procainamide (hallucinations, hysteria), quinidine (severe gastrointestinal side effects) and disopyramide (mild and transient paresthesia of the arms). In patient 1 in group 4, maternal therapy was initiated for fetal tachycardia. The mother developed skin rash and mild thrombocytopenia after 15 days, and therapy was withdrawn.

The possibility of serious side effects could not be totally excluded in 3 patients. Patient 8 in group 3 developed chest radiographic findings suggesting pulmonary toxicity, which retrospectively was determined to represent worsening heart failure. Amiodarone was discontinued, and the patient subsequently underwent successful cardiac transplantation. Two patients with underlying heart disease and poor ventricular function before amiodarone treatment died from congestive heart failure during amiodarone therapy (patient 15, group 2; patient 6, group 3). No patients had thyroid or liver dysfunction.

Absence of adverse effects: No patient required pacemaker implantation during amiodarone therapy. In 3 patients with atrioventricular block or sinus bradycardia, or both, pacemakers had been implanted 3 to 5 years before amiodarone therapy. In 2 patients, pacemakers were implanted after discontinuation of amiodarone treatment: an antitachycardia pacemaker in 1 patient and a ventricular demand pacemaker in the other for symptomatic bradycardia after additional surgery.

Patients 3 and 8 in group 3 received amiodarone for 2 and 14 months, respectively, before cardiac transplantation. Both patients underwent successful cardiac transplantation without any apparent deleterious side effects from amiodarone.

Combined antiarrhythmic therapy: Twelve patients received additional antiarrhythmic drugs other than digoxin in an effort to achieve better tachycardia control. In 10 of these patients amiodarone was ineffective but was continued, whereas in the remaining 2 amiodarone was ineffective and was withdrawn. Combined therapy lasted from 0.1 to 2 years (Table V). Beta-blocking drugs (propranolol or metoprolol) and mexiletine were administered to 3 patients from group 1. Beta-blocking drugs were given with amiodarone in 2 patients from group 2. In 1 patient who had taken metoprolol alone

for 5 years, a cardiac arrest with documented ventricular fibrillation developed after 2 weeks of combined amiodarone-metoprolol therapy; no further cardiac arrests have occurred since amiodarone was discontinued. Verapamil or class Ia antiarrhythmic drugs, or both, were used in association with amiodarone in 7 patients from group 4.

Short-term therapy in infants: Seven infants (ages <18 months) received amiodarone alone or in combination with other drugs for <18 months. After discontinuation of amiodarone, no patient had tachycardia recurrence during follow-up of 4 months to 2 years.

Patients 1 and 3 in group 1 had incessant ventricular tachycardia and received amiodarone in combination with mexiletine and propranolol for 5 and 16 months, respectively. After a tachycardia-free period of 4 to 8 months, the drugs were discontinued and the patients remained in normal sinus rhythm during >2 years of follow-up.

In group 4, therapy was discontinued in 5 patients in <18 months. Patient 1 presented with fetal tachycardia and severe hydrops fetalis with left ventricular shortening <10%. Tachycardia was unresponsive to maternally administered digoxin, verapamil or quinidine sulfate, but conversion to normal sinus rhythm occurred after 5 days of amiodarone treatment. Amiodarone was discontinued after 15 days. The fetus recovered from hydrops fetalis and did not have recurrences of tachycardia for the remaining 15 weeks of gestation. After birth, orthodromic-reciprocating tachycardia was induced during transesophageal pacing, but the neonate was discharged without antiarrhythmic therapy because spontaneous postnatal tachycardia was not observed. Patient 2 received amiodarone for 2 months because of chaotic atrial tachycardia. During 4 months of follow-up without therapy, no tachycardia episodes were observed. Patient 5 presented as a newborn with congestive heart failure due to orthodromic reciprocating tachycardia. After unsuccessful drug trials with procainamide, flecainide and verapamil, amiodarone therapy in combination with verapamil was begun. After 6 tachycardia-free months, amiodarone was withdrawn while verapamil was continued for 3 additional months. Patient 6 presented with congestive heart failure and atrial ectopic tachycardia, and received amiodarone for a total of 10 months. After a tachycardia-free period of 5 months, amiodarone was discontinued. The patient remained in normal sinus rhythm during 7 months of follow-up. Patient 7 had incessant reciprocating tachycardia; after 4 unsuccessful drug trials (verapamil, propranolol, procainamide and digoxin), the patient received amiodarone (in combination with procainamide, verapamil and digoxin for 1 month) for a total of 6 months. The patient developed sinus rhythm after 1 month of treatment and amiodarone was contin-

ued as the sole therapy. After a tachycardia-free period of 4 months, amiodarone was discontinued and the patient has remained tachycardia-free during 8 months of follow-up.

DISCUSSION

Amiodarone is a class III antiarrhythmic drug (increases the action potential duration and refractoriness) but also has significant class I, calcium antagonist and β -receptor blocking properties. With the usual oral administration protocol, amiodarone has a significant antiarrhythmic action within the first 2 weeks of treatment,^{1,12} even though class III effects (increase in ventricular refractoriness) reach their maximal values after 10 weeks.¹² Because of this delay in onset of amiodarone effect, it may be advantageous to use amiodarone in combination with other agents.

Based on the results of this study, amiodarone may be effective as part of combined therapy in pediatric patients. As a single agent, amiodarone does not appear effective in postoperative patients with primary atrial tachycardia requiring cardioversion, but it may be the treatment of choice in similar patients with recurrent spontaneously terminating bouts of primary atrial tachycardia. Amiodarone should be considered for use in young patients with recurrent syncope when ventricular ectopy is present. Finally, in infants <18 months old with either electrocardiographically documented ventricular tachycardia or recurrent supraventricular tachycardia refractory to conventional therapy, amiodarone may be the treatment of choice owing to both the convenient amiodarone dosing schedule and the favorable natural history of rhythm disturbances in this age group. Life-threatening side effects were observed in 2 patients. Other side effects were less serious. Importantly, no patient required cardiac pacing during amiodarone therapy, and previous amiodarone administration did not preclude successful cardiac transplantation in 2 patients.

Several reports have suggested that amiodarone may be the treatment of choice for specific rhythm disturbances in young patients.^{2,3,13-15} An important question is how to reconcile enthusiastic use of amiodarone for these conditions with the admonition that amiodarone only be used "for young patients with life-threatening arrhythmias that are resistant to conventional drugs."⁵ In this context, it is important to examine the natural history of rhythm disturbances in pediatric patients. It has previously been shown that for ectopic atrial tachycardia in pediatric patients of all ages,¹⁴ atrial flutter in neonates,¹⁶ orthodromic reciprocating tachycardia in infants,¹⁷ and certain types of ventricular tachycardia,¹⁵ patients lose the capacity to have spontaneous tachycardia and may not have recurrences even later in life. For example, 32% of infants with or-

thodromic-reciprocating tachycardia no longer have inducible tachycardia by age 1 year¹⁷ and many others may not have spontaneously occurring tachycardia for more than a decade.¹⁸ In such patients, short-term use (<18 months) of amiodarone could be anticipated to be sufficient treatment, as illustrated by the 7 infants we studied who received amiodarone as short-term therapy.

It has been suggested that amiodarone treatment outcome be described as failure, partial success or complete success.³ Although it is relatively easy to observe the failure (ineffectiveness) of an antiarrhythmic drug, it is much more difficult to assess its effectiveness,¹⁴ which depends on the frequency of arrhythmia episodes before therapy and on the method and length of follow-up. In our retrospective study, we deemed a recurrence of tachycardia or symptoms during treatment as ineffective treatment. Amiodarone was considered effective when the drug appeared to control the tachycardia or prevent symptoms. In trying to assess therapeutic benefits, we found the concept of "useful," including patients in whom amiodarone was considered effective or ineffective but was continued, to be more practical than success or failure. We found amiodarone to be clinically useful in 68% of patients. This usefulness was achieved in 45% of patients receiving amiodarone as a sole agent and in 23% of patients receiving amiodarone as part of combination therapy.

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Effects of Enflurane on Inducibility of Ventricular Tachycardia

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The effects of enflurane on cardiac electrophysiologic parameters and on inducibility of ventricular tachycardia (VT) by programmed stimulation were studied in 12 patients (11 men, 1 woman, mean age \pm standard deviation 55 ± 8 years) with drug refractory sustained monomorphic VT who underwent transcatheter ablation with high-energy direct-current shocks. One catheter ablation procedure was performed in 10 patients, whereas 2 ablation sessions were necessary in 2 patients. Programmed ventricular stimulation was performed on 2 separate days (mean interval 19). There were 2 baseline studies, 1 several days before ("baseline study I") and the second at the beginning of the ablation procedure ("baseline study II") while the patient was awake and nonsedated. The third programmed stimulation study was done 15 to 30 minutes after administration of anesthesia with enflurane, oxygen and nitrous oxide ("enflurane study"). Rate of sinus rhythm, QRS duration, PQ interval and ventricular effective refractory period were unaltered, whereas QTc interval increased significantly after initiation of anesthesia. Before and after induction of general anesthesia, clinical VT was inducible in all patients. However, in 1 patient, induction of VT was only possible by pacing in the left ventricle after enflurane administration. Based on these data, it is concluded that general anesthesia with enflurane, oxygen and nitrous oxide has no marked influence on inducibility of clinical VTs. Therefore, this type of anesthesia may be useful for nonpharmacologic, ablative procedures requiring general anesthesia.

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Many anesthetic agents have effects on cardiac electrophysiologic parameters owing to either direct action on the myocardium or to their indirect influence on the sympathetic nervous system, which is of critical importance in the regulation of heart rate, myocardial function and peripheral vascular resistance. These effects do not play a role in clinical electrophysiologic studies of awake and nonsedated patients.¹⁻⁴ However, intraoperative mapping of supraventricular and ventricular tachycardias (VTs) is performed under general anesthesia. Studies in patients undergoing surgical treatment of recurrent sustained VT or ventricular fibrillation, or both, have shown that, in addition to other factors, general anesthesia may decrease the inducibility of ventricular tachyarrhythmias.⁵⁻¹² Recent experimental studies have investigated the inducibility of VT after administration of anesthetic drugs.¹³⁻¹⁸ However, there are no systematic studies available on humans. Therefore, we evaluated the effects of general anesthesia with enflurane, oxygen and nitrous oxide using high-energy direct-current shocks in 12 patients with recurrent monomorphic sustained VT undergoing catheter ablation procedures.

METHODS

In 12 patients (Table I) (11 men and 1 woman, mean age \pm standard deviation 55 ± 8 years, range 48 to 71) with recurrent monomorphic sustained VT, a total of 14 catheter ablation procedures were performed (1 procedure in 10 patients, 2 procedures in 2 patients).

Nine patients had coronary artery disease with a history of previous myocardial infarction; 6 of these had had an inferior wall infarction and 3 had had an anterior wall infarction. Of the remaining 3 patients, 1 had arrhythmogenic right ventricular disease, 1 presented with dilated cardiomyopathy and 1 had aortic valvular heart disease. The mean ejection fraction in patients with coronary artery disease and dilated cardiomyopathy was $36 \pm 9\%$. Two patients with coronary artery disease had undergone previous cardiac surgery and 1 of these had failed to respond to map-guided antitachycardia surgery.

All patients had a history of recurrent sustained monomorphic VT refractory to class I or III antiarrhythmic drugs. In all 12 patients, at least several episodes of sustained VT had been recorded by 12-lead

TABLE I Clinical Characteristics of 12 Patients with Drug-Resistant Ventricular Tachycardia Who Underwent Direct-Current Catheter Ablation

Pt. No.	Age (yr) & Sex	Diagnosis	EF (%)	Arrhythmia
1	60 M	CAD	35	Incessant VT
2	55 M	VHD	65	CRVT
3	67 M	CAD	35	CRVT
4	50 M	CAD	—	CRVT
5	62 M	CAD	36	Incessant VT
6	46 M	DC	65	CRVT
7	71 M	CAD	37	CRVT
8	52 M	CAD	33	CRVT
9	48 M	ARVD	64	CRVT
10	48 F	CAD	22	CRVT
11	54 M	CAD	36	CRVT
12	49 M	CAD	28	CRVT

ARVD = arrhythmogenic right ventricular disease; CAD = coronary artery disease; CRVT = chronic recurrent VT; DC = dilated cardiomyopathy; EF = ejection fraction; VHD = valvular heart disease; VT = ventricular tachycardia.

electrocardiogram on which the diagnosis of "clinical VT" was based. The median number of episodes of sustained VT before catheter ablation was 10 (range 1 to 40). Eight patients had 1 VT morphology, 2 patients had 2, 1 patient had 5 and 1 patient had 6. Previous antiarrhythmic drug therapy was unsuccessful in all patients. Seven patients (58%) had unsuccessful long-term therapy involving amiodarone alone or in combination with class I antiarrhythmic agents. At the time of catheter ablation, 4 patients had no antiarrhythmic therapy, whereas the remaining 8 patients were receiving drug therapy. Seven patients were treated with amiodarone, 2 with class I antiarrhythmic drugs and 1 with sotalol. These drugs were administered to further slow VT to allow a detailed mapping or, in the case of amiodarone, because of its long elimination half-life.

Programmed ventricular stimulation was performed at the right ventricular apex using bipolar electrode catheters. Single and double premature stimuli were applied during sinus rhythm and during paced ventricular drives at cycle lengths of 500, 430, 370 and 330 ms until sustained VT was induced. If VT was not inducible with this protocol, triple premature stimuli were used at a basic drive of 500 ms. All patients had inducible VT at the right ventricular apex. Stimulation at the right ventricular outflow tract was not part of the protocol. The end point of stimulation was either the induction of sustained VT or the completion of the entire pacing protocol.

Endocardial catheter mapping was performed after intravenous administration of heparin. Quadripolar electrode catheters were used (USCI 6Fr or USCI Josephson). A bipolar electrode catheter was placed in the right ventricular apex (Cordis 5Fr). The techniques of catheter mapping and catheter ablations have been described previously.¹⁸ During the first step of the mapping procedure, electrograms during induced VT were

recorded at multiple sites at the left or, when indicated, the right ventricle using biplane fluoroscopy. Then, a more detailed mapping was performed at an area that was identified as showing the earliest presystolic activation.

Induction and maintenance of anesthesia were performed according to a well-established protocol. After administration of thiopental (3 to 5 mg/kg) or etomidate (0.15 to 0.3 mg/kg), the patients were relaxed and intubated. Anesthesia was maintained with enflurane at an end-expired concentration of 0.5 to 1.0 minimum alveolar anesthetic concentration in an oxygen (30%)-nitrous oxide (70%) mixture. Patients were ventilated at a rate of 10 to 16 ventilations per minute, with a tidal volume of 12 to 15 ml/kg. Respiration was controlled to maintain partial pressure of carbon dioxide and pH within normal limits. Arterial blood pressure was continuously monitored.

Sustained VT was defined as monomorphic VT lasting >30 seconds or requiring termination before this time because of hemodynamic compromise. Clinical VT was defined as VT identical in morphology to documented spontaneous VT. Differences in heart rate ± 20 beats/min were accepted as still representing clinical VT if no differences in morphology occurred. Inducibility of VT was considered to be unchanged if VT was initiated at the same basic drive cycle length as that during the control study. Inducibility was considered to be changed if VT was elicited at a basic drive different from the control rate. Differences in the mode of induction were classified as "one step more difficult" for VT induced at a rate 20 beats/min higher than the control rate and as "one step easier" for VT induced at a rate 20 beats/min lower than the control rate.

Programmed ventricular stimulation was performed on 2 separate days with a mean interval of 19 days (range 2 to 62) between studies. Thus, there were 2 baseline studies; the first while the patient was awake and nonsedated several days before the ablation procedure ("baseline study I") and the second at the beginning of the ablation procedure ("baseline study II"). Fifteen to 30 minutes after initiation of general anesthesia, the third programmed stimulation study ("enflurane study") was performed before the first shock was delivered. The same stimulation protocol was used for each of the 3 studies.

In patients in whom a second ablation procedure was attempted, the results of baseline study I were compared with baseline study II and the enflurane study.

The following parameters were analyzed: electrocardiographic data (PQ interval, QRS duration, QTc interval and cycle length of sinus rhythm); mode of VT induction; morphology; cycle length; and mode of termination of VT. All measurements were obtained be-

fore the beginning of programmed ventricular stimulation in awake, nonsedated patients or 15 to 30 minutes after induction of general anesthesia, or both.

Statistical analysis: Data were compared with Student's paired *t* test. A *p* value <0.05 was considered significant. All data are expressed as mean \pm standard deviation.

RESULTS

The inducibility of VT was unchanged in 11 of 12 (92%) patients and was one step more difficult in 1 (Figure 1). Baseline study I was not performed in 2 patients with incessant VT. VT was elicited with the same number of premature stimuli in 8 patients. In the remaining 4 patients, the number of extrastimuli required for induction of arrhythmia changed; the basic drive cycle length was the same in 3, but changed in 1 from 500 to 430 ms (Figure 2).

During the 2 baseline studies, the cycle length of induced VT (376 ± 61 to 367 ± 72 ms, *p* = not significant [NS]) and the effective refractory period of the right ventricular apex at a paced cycle length of 500 ms were not different (254 ± 26 to 255 ± 19 , *p* = NS).

The morphologies of VT were identical in 10 patients but different in 2. These 2 patients had several different clinical VT morphologies.

During baseline study I, VT was terminated by rapid ventricular pacing in 11 patients and by direct-current shock in 1, whereas no VT required termination by external cardioversion during baseline study II.

During general anesthesia, VT was inducible in 13 of 14 studies (93%) by programmed ventricular stimulation at the right ventricle. In 1 study, the induction of VT was only possible by pacing the left ventricle. The mode of induction of VT was unchanged in 12 of 13 studies (92%) (Figure 1). In the remaining study, VT

TABLE II Electrophysiologic Findings Before (baseline study II) and During (enflurane study) General Anesthesia

	Baseline Study II	Enflurane Study	
QRS (ms)	113 \pm 21	113 \pm 22	NS
PQ (ms)	188 \pm 20	189 \pm 20	NS
QTc (ms)	456 \pm 51	482 \pm 57	<i>p</i> < 0.05
SR (beats/min)	80 \pm 18	83 \pm 22	NS
ERP-V (ms)	255 \pm 19	269 \pm 34	NS
VT-CL (ms)	367 \pm 72	389 \pm 67	NS

ERP-V = effective refractory period of right ventricle; NS = not significant; SR = sinus rhythm; VT-CL = cycle length of ventricular tachycardia.

was induced by 2 premature stimuli during sinus rhythm in baseline study II, but after general anesthesia; the same VT was reproduced by pacing at 500 ms and application of 1 premature stimulus.

The number of extrastimuli necessary to induce VT was identical in 10 of 13 (77%) studies (Figure 2). In 3 studies, VT was induced by 2 premature stimuli during baseline study II and by only 1 premature stimulus after induction of general anesthesia. The basic drive cycle length to induce VT was the same in 2 patients and changed in 1. The morphologies of VT were similar during 12 ablation procedures and different in 2 patients having 5 and 6 morphologies of clinical tachycardia, respectively, before catheter ablation. The cycle length of VT was longer after induction of anesthesia, but this difference was not statistically significant (367 ± 72 and 389 ± 67 ms, *p* = NS). Rapid ventricular pacing terminated VT in 11 patients before and in 10 after induction of anesthesia, whereas in the remaining 2 patients VT terminated spontaneously after 30 seconds (during anesthesia). There were no cardioversions necessary to terminate VT during baseline study II, but after general anesthesia, VT had to be terminated with external direct-current shock in 2 patients because of hemodynamic compromise.

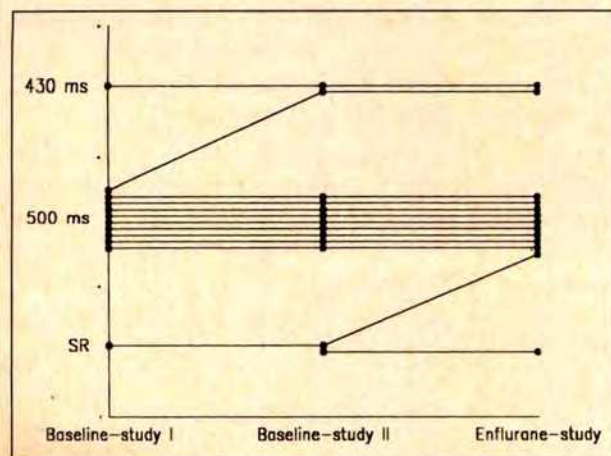


FIGURE 1. Induction mode of ventricular tachycardia by programmed ventricular stimulation during 2 conscious studies (Baseline-study I and Baseline-study II) and during general anesthesia (Enflurane-study) dependent on paced basic drive cycle lengths. SR = sinus rhythm.

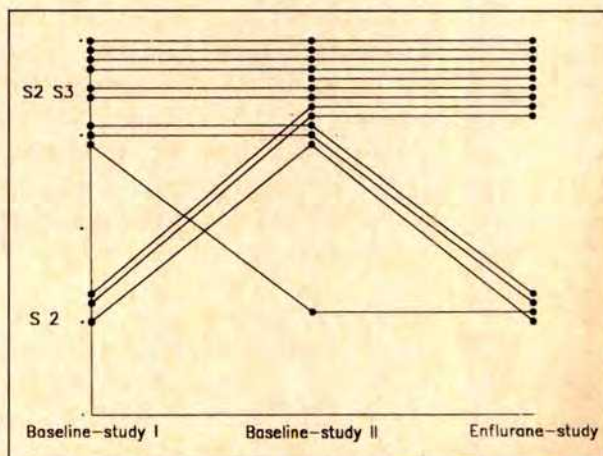


FIGURE 2. Induction mode of ventricular tachycardia by programmed ventricular stimulation during two conscious studies (Baseline-study I and Baseline-study II) and during general anesthesia (Enflurane-study) dependent on number of premature stimuli. S = stimulus.

Effects on electrophysiologic parameters (Table II):

The effects of general anesthesia were assessed by comparing measurements during baseline study II and the enflurane study. The rate of sinus rhythm, PQ interval and QRS duration were not changed. QTc interval increased significantly from 456 ± 51 to 482 ± 57 ms ($p < 0.05$), and the ventricular effective refractory period at a paced cycle length of 500 ms increased from 255 ± 19 to 269 ± 34 ms ($p = \text{NS}$).

DISCUSSION

Reproducibility of VT induction by programmed ventricular stimulation is a major prerequisite for catheter ablation because detailed mapping during VT is mandatory. The application of direct-current high-energy shocks through electrode catheter is only possible under general anesthesia.¹⁹ However, many anesthetic agents alter the electrophysiologic parameters of the heart and may hereby influence the induction of VT.^{15,16}

Previous studies have reported that VT remains inducible in 30 to 90% of patients during map-guided surgery. As well as other factors, anesthesia may influence the inducibility of VT. Bitar et al¹³ reported on 2 patients with life-threatening VT unresponsive to antiarrhythmic therapy who were successfully treated with general anesthesia using intravenous lorazepam and morphine sulfate. Hunt and Ross¹⁴ compared the effects of 3 anesthetic agents on induction of VT in infarcted dogs. Halothane and pentobarbital suppressed the inducibility of VT in 40 to 50% of the dogs. In contrast, a neuroleptic combination of fentanyl-droperidol plus nitrous oxide caused no significant change in the inducibility or character of VT.

There are no detailed studies on the inducibility of VT during inhalational anesthesia in humans. Nevertheless, experimental studies have shown that the inducibility of atrial tachycardia and VT decreased with programmed stimulation in dogs narcotized with halothane.^{14,17,18} In this study, the effects of general anesthesia, using enflurane, oxygen and nitrous oxide, on cardiac electrophysiologic parameters and on inducibility of VT were studied. Using enflurane, an inhalational anesthetic drug that has a negative effect on myocardial contractility, depresses peripheral vascular resistance, but does not sensitize the myocardium to catecholamines in contrast with halothane.

Except for QT interval, the electrophysiologic parameters did not differ after anesthesia. However, QTc increased significantly when evaluated before and during anesthesia, as previously reported.²¹

Halothane and enflurane cause similar dose-dependent prolongations of atrioventricular nodal conduction time and refractoriness in anesthetized dogs.^{1,14,20} In

this study, there was no prolongation in atrioventricular conduction during anesthesia using enflurane in an end-expired concentration of 0.5 to 1.0 minimum alveolar anesthetic concentration. However, this does not reflect the refractory period of the atrioventricular node, but suggests that enflurane may also be used during catheter ablation of supraventricular tachycardia with direct-current high-energy shocks.

Halothane slows intramyocardial conduction.² Therefore, inhalational narcotic drugs would be expected to change the modality of VT induction and to increase VT-cycle lengths. Halothane has also been shown to suppress induction of tachyarrhythmias by programmed stimulation in experimental studies.^{14,17,18} VT was inducible in only 50%¹⁴ and 65%¹⁸ of dogs. In this study, anesthesia caused no marked change in inducibility of VT. VT was inducible by programmed stimulation at the right ventricle in 13 of 14 (93%) ablation procedures and in 1 patient by pacing in the left ventricle.

Denniss et al¹⁸ stated that their inability to induce ventricular tachyarrhythmias with halothane was due to an increase in the ventricular effective refractory period, which prevented the use of short extrastimulus coupling intervals. There was no significant increase in the effective refractory period after induction of anesthesia. Nevertheless, we did not need a shorter extrastimulus coupling interval to induce VT during anesthesia. There was also no marked difference in the mode of VT induction. The basic drive rhythm was unchanged in 92% of studies and the number of extrastimuli was unchanged in 77%.

In contrast to experimental studies in chronically instrumented dogs narcotized with halothane,¹⁴ the rate of induced VT did not change significantly as a consequence of anesthesia. This may reflect an unaltered ventricular conduction time. There were no changes in morphology of induced VT in 10 of 12 (83%) patients, whereas the 2 remaining patients had 5 and 6 clinical morphologies of VT, respectively. Ventricular fibrillation was not induced in any patient.

Based on these data, we conclude that general anesthesia with enflurane, oxygen and nitrous oxide has no marked influence on inducibility of clinical VT. Therefore, this anesthetic drug regimen can be used especially during map-guided antitachycardia surgery and transcatheter ablation procedures, where inducibility of VT is a prerequisite.

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Dispersion of Ventricular Repolarization in the Long QT Syndrome

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To identify markers of dispersion of the ventricular repolarization in the idiopathic long QT syndrome, body surface potential maps were analyzed in 40 such patients (mean age \pm standard deviation 21 ± 11 years) and in 30 healthy control subjects (mean age 24 ± 7 years). In each subject, 117 chest leads were recorded and maps of the integral values of the QRST interval were calculated. A multipolar distribution of the values, a marker of gross electrical inequalities of repolarization, was found only in 4 patients. To detect minor regional disparities of ventricular recovery, all the ST-T waveforms were analyzed in each subject. The ST-T waves were represented by a discrete series of potential values. The "similarity index" was computed by applying a principal component analysis, which represents (in percent) to what extent 1 fundamental pattern of ST-T reproduces all the recorded waveforms. The mean value of the similarity index was significantly lower in patients with long QT syndrome than in control subjects (49 ± 10 vs $77 \pm 8\%$, $p < 0.0001$). A value $< 61\%$ (corresponding to 2 standard deviations below the mean value for controls) was found in 35 of 40 patients and in only 1 control subject (sensitivity 87%, specificity 96%). Thus, the similarity index is a more sensitive marker than the multipolar distribution of QRST integral maps in revealing electrical disparities of the ventricular recovery times. The low value of the similarity index found in patients with long QT syndrome indicates a large variety of ST-T waveforms, suggesting a high degree of dispersion of ventricular recovery times, which is a condition of vulnerability to malignant ventricular arrhythmias.

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The electrophysiologic mechanisms for vulnerability to malignant ventricular arrhythmias in the idiopathic long QT syndrome are still debated, and both reentry and triggered activity have been proposed.¹ In general, it has been demonstrated that a greater than normal disparity of recovery times in cardiac muscle is associated with enhanced vulnerability to arrhythmias.²⁻⁵ The recovery process of myocardial fibers is greatly influenced by sympathetic activity,⁴ and regional variations in sympathetic drive result in local changes of recovery times.⁶ The latter condition could exist in the long QT syndrome, in which an imbalance of the sympathetic innervation of the heart has been hypothesized.^{1,7} The detection of electrical disparities in the ventricular recovery process from the body surface presents difficulties and several methods have been proposed.⁸⁻¹⁴ We have attempted to identify markers of electrical disparities of the ventricular recovery in patients with idiopathic long QT syndrome by analyzing body surface potential maps.

METHODS

Study group: A group of 70 subjects, 40 patients with idiopathic long QT syndrome and 30 healthy control subjects, was studied. The 40 patients with long QT syndrome consisted of 26 female and 14 male patients aged 6 to 50 years (mean 21 ± 11) (Table I). The diagnosis of long QT syndrome was based on the presence of an abnormally prolonged QT interval ($QT_c > 440$ ms) accompanied by either a history of syncope/cardiac arrest or by the presence of long QT syndrome in other family members.⁷ In 3 patients QT_c was within normal limits, but they were considered to have long QT syndrome based on the presence of documented syncopal episodes together with other family members affected by long QT syndrome. Twenty-nine patients were symptomatic, i.e., they had had syncopal episodes or cardiac arrest; 11 patients were asymptomatic. All the 29 symptomatic patients receiving long-term β -adrenergic blocking therapy. Two asymptomatic patients were also treated with β blockers.

Thirty healthy subjects, 15 male and 15 female subjects, aged 7 to 40 years (mean 24 ± 7), were also studied as controls (Table II). None had a history of cardiac disease; physical examination and a 12-lead electrocardiogram were within normal limits.

TABLE I Characteristics of the Patients with Long QT Syndrome

Pt. No.	Age (yr) & Sex	QTc (ms)	HR (beats/min)	Symptoms* Familial†	Therapy	QRST I-Map	SI (%)
1	6 F	453	75	+/+	BB	Neg.	41
2	8 F	490	61	+/+	BB	0	33
3	8 F	574	72	+/+	BB	Mul.	53
4	10 F	467	65	+/+	BB	Neg.	63
5	11 F	711	51	+/+	BB	Neg.	32
6	11 F	550	84	+/+	BB	Mul.	39
7	11 M	549	72	+/+	BB	0	49
8	11 F	456	64	+/+	BB	Neg.	45
9	13 M	470	44	+/+	BB	Neg.	31
10	14 F	435	44	+/+	BB	Neg.	54
11	15 M	520	57	+/+	BB	Mul.	52
12	17 M	458	69	+/+	BB	0	49
13	18 M	530	62	+/+	BB	0	62
14	19 F	470	74	+/+	BB	Neg.	49
15	19 F	466	59	+/+	BB	Neg.	46
16	19 M	524	67	+/+	BB	0	49
17	19 F	495	60	+/+	BB	0	55
18	20 F	477	57	+/+	BB	Neg.	42
19	20 F	510	54	+/+	BB	Neg.	55
20	21 F	424	77	+/+	BB	0	57
21	21 F	500	50	+/0	BB	Neg.	41
22	22 F	518	80	+/+	BB	Neg.	38
23	25 F	435	58	+/+	BB	Neg.	58
24	27 F	650	50	+/+	BB	0	61
25	27 F	500	66	+/+	BB	Neg.	60
26	28 F	460	63	+/+	BB	0	43
27	30 F	470	76	+/0	BB	Neg.	54
28	33 F	530	60	+/+	BB	Neg.	43
29	37 F	460	66	+/+	BB	0	57
30	10 M	540	56	0/+	0	0	41
31	10 M	460	50	0/+	0	0	49
32	11 M	465	96	0/+	0	0	47
33	13 M	480	56	0/+	BB	Mul.	35
34	17 M	456	50	0/+	0	Neg.	62
35	20 F	455	60	0/+	BB	0	73
36	32 M	462	67	0/+	0	Neg.	53
37	34 F	520	68	0/+	0	0	53
38	44 M	484	85	0/+	0	Neg.	68
39	44 M	464	52	0/+	0	Neg.	46
40	50 F	469	57	0/+	0	Neg.	36

*Syncope or cardiac arrest.

†Long QT syndrome in other family members.

BB = β blockers; HR = heart rate; I-Map = integral map; Mul. = multipolar distribution of the integral values; Neg. = large anterior negativity; 0 = no apparent abnormality; SI = similarity index.

Body surface potential mapping: By means of vertical rubber straps, 117 silver-silver chloride electrodes were applied to the anterior and posterior chest. The probes were positioned as shown in Figure 1, i.e., 90 on the anterior chest wall and 27 on the back of each subject. Wilson's central terminal was taken as the reference point for measurement of chest potentials. The 117 chest leads were recorded and converted in digital format with a sampling rate of 500 Hz per channel and stored on disk. The data were then processed on a IBM AT computer.

Integral maps: The procedure for obtaining integral maps has been described in a previous study.¹⁵ Briefly, at each lead point the potential \times time integral relating to the QRST interval was calculated as an algebraic sum of all instantaneous potentials multiplied by the sampling interval (2 ms). The values in microvolts \times seconds were transferred to a diagram representing the

thoracic surface (integral map); then isointegral contour lines were drawn manually.

Similarity index: In each subject the morphology and amplitude of the 117 ST-T waveforms were analyzed. The ST-T waveform was divided into successive 20-ms intervals (Figure 2) and the mean potential value of each interval was considered, thus minimizing the noise due to the 50-Hz power line interference. To eliminate the influence of the baseline drift we subtracted the value of the preceding interval from the mean potential value of each interval; this allows us to deal with increments instead of absolute values. Thus, each ST-T waveform is represented by a discrete series of 15 to 25 values (Figure 2).

In each subject a principal component analysis¹⁶ of the original 117 sets of values was performed. This analysis allowed the identification of 1 set of values, corresponding to the "first principal component," which

TABLE II Characteristics of the Control Subjects

Pt. No.	Age (yr) & Sex	QRST I-Map	SI (%)
1	7 M	0	74
2	9 F	0	62
3	14 M	0	72
4	16 F	0	73
5	18 F	0	78
6	19 F	0	74
7	19 F	0	78
8	20 F	0	75
9	20 F	0	64
10	22 F	0	69
11	23 F	0	77
12	24 M	0	80
13	24 M	0	80
14	24 F	0	88
15	25 M	0	78
16	26 F	0	81
17	26 N	Neg.	90
18	26 F	0	82
19	27 M	0	80
20	27 M	0	74
21	27 F	0	77
22	28 F	Neg.	55
23	28 M	0	91
24	28 M	0	77
25	29 M	0	76
26	30 M	0	86
27	31 M	0	73
28	33 M	0	82
29	40 M	0	82
30	40 F	0	77

Abbreviations as in Table I.

better represents, by means of appropriate multiplication factors (1 factor for each recording lead) as described by Kleinbaum et al,¹⁶ most of the 117 sets of values recorded in that subject. Therefore, the ratio between the information content of the first principal component and the total variation (i.e., information) of the original data indicates the ability of 1 single waveform (first principal component) to reproduce all the

recorded waveforms. We defined this ratio, expressed in percent, as the "similarity index" (SI), i.e.:

$$SI = \frac{\text{1st Principal Component}}{\text{Total Variation}} \%$$

A high value of similarity index indicates a great similarity of all waveforms to 1 fundamental waveform, i.e., a great similarity of all the waveforms to each other. In contrast, a low value of the similarity index indicates a large variety of ST-T waveforms, and this is considered a marker of repolarization disparities.

In each control subject and patient with a long QT syndrome, the similarity index was calculated for at ≥ 2 different cardiac beats; the mean value was then considered. The mean difference of all the within-subject measurements of similarity index was small, i.e., $2.2 \pm 1.3\%$ in the control group and $3.2 \pm 3.6\%$ in the group with long QT syndrome.

Statistical analysis: A comparison between group means was performed by the Wilcoxon test for unpaired data and by the chi-square analysis, when appropriate. Data are expressed as mean \pm 1 standard deviation.

RESULTS

QRST integral maps: In all control subjects, the integral maps showed a bipolar distribution of the integral values with a minimum in the upper sternal-right clavicular area and a maximum in the left mammary-axillary region (Figure 3). This is the typical pattern for normal subjects.^{13,15,17,18} In 2 control subjects, the negative values entirely or almost entirely covered the anterior right thorax.

Among patients with long QT syndrome, 4 (10%) had a multipolar distribution of the QRST integral values: 3 patients had 1 maximum and 2 minimum distri-

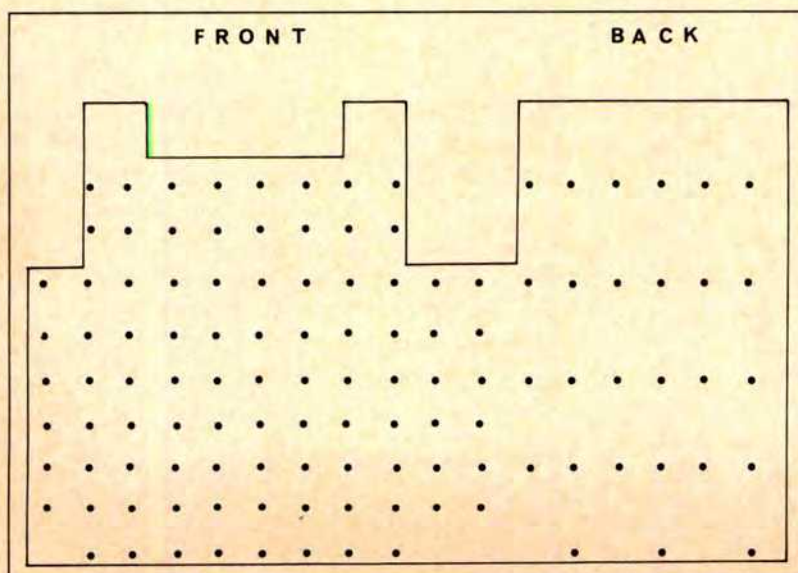


FIGURE 1. Schematic drawing illustrating the anterior and posterior chest surface. The electrode sites are indicated by dots: 90 are located from the right midaxillary line to the left posterior axillary line; 27 are on the back.

butions; 1 patient had 2 maximum and 1 minimum distribution.

In the remaining 36 patients the distribution of the integral values was bipolar. In 15 patients (37%), the QRST integral maps showed a location of the maximum and minimum within normal limits. Figure 4 illustrates the QRST integral map of a patient with symptomatic long QT syndrome with a normal ST-T pattern and only a slight QTc prolongation in the electrocardiogram: the minimum is located in the right subscapular area and the maximum in the left mammary region. In the other 21 patients (53% of the cases), the location and the size of the negative area were abnormal. These patients had a larger than normal area of negative values on the anterior thorax, a pattern already described in patients with long QT syn-

drome.¹⁵ Figure 5 shows the typical case of a patient whose T waves were negative in V₁, biphasic in V₂ and notched in V₃; the minimum is located in the lower sternal area and the negative values almost entirely cover the anterior chest surface. Mean values for the maximum and minimum were not significantly different in the control group and group with long QT syndrome.

Similarity index: The mean value of the similarity index was markedly lower in patients with long QT syndrome than in control subjects ($49 \pm 10\%$ vs $77 \pm 8\%$; $p < 0.00001$). The individual values of the similarity index in the control group and the group with long QT syndrome are illustrated in Figure 6. There is a clear-cut separation between the 2 groups with minimal overlapping. We considered a value of 61% as a cutoff point, which represents 2 standard deviations below the

FIGURE 2. Schematic drawing of QRS ST-T waveforms. The ST-T wave is subdivided into 20-ms intervals (upper tracing). The lower tracing is amplified; the ST-T wave is defined by a series of 15 potential values (arrows).

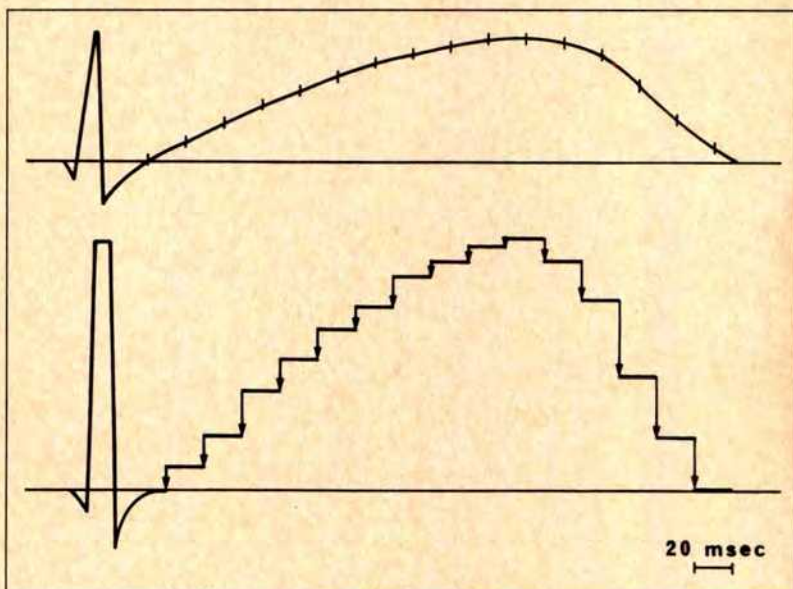
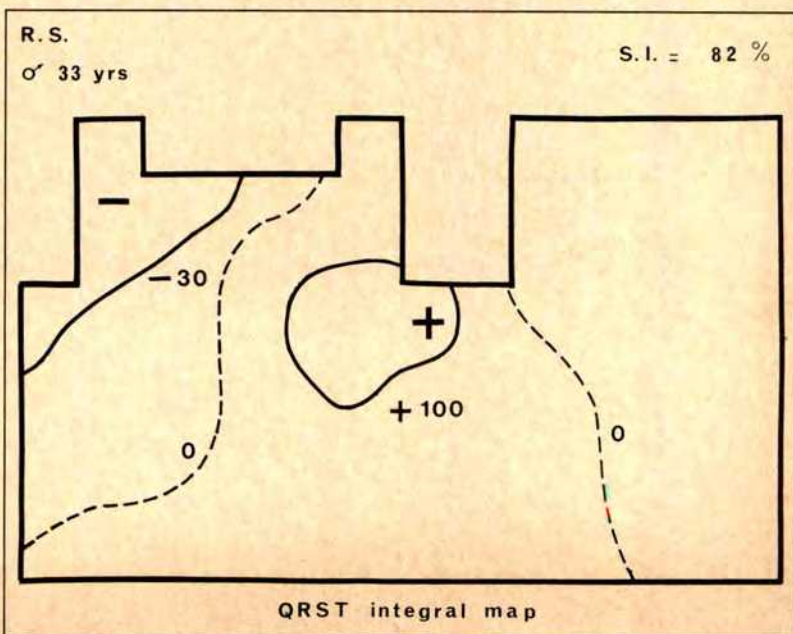


FIGURE 3. QRST integral map from a 33-year-old healthy man, showing the typical normal pattern. The values are expressed in microvolts \times seconds. Similarity index (S.I.) is 82%.



mean value for the control group, and we found that most (35 of 40) patients with long QT syndrome had a lower value, whereas only 1 control subject had a value below this threshold (chi-square, $p < 0.0005$; sensitivity 87%, specificity 96%). Thus, among patients with long QT syndrome, significant abnormalities were observed much more frequently (87 vs 10%) by calculating the similarity index (value $< 61\%$) than by examining the QRST integral maps (multipolarity). The similarity index was not different between symptomatic and asymptomatic patients (48 vs 51%).

DISCUSSION

This study demonstrates that the similarity index is more sensitive than the multipolar distribution of QRST integral maps in revealing abnormalities of surface repolarization potentials, which can be related to electrical disomogeneity of the ventricular recovery process. Specifically, the low value of the similarity index found in patients with long QT syndrome indicates

a large variety of ST-T waveforms, and suggests a high degree of dispersion of ventricular recovery times, a condition that enhances vulnerability to malignant ventricular arrhythmias.

Ventricular repolarization disparities: The QRST integral maps contain valuable information on the ventricular recovery process.¹⁹⁻²¹ Areas of QRST deflections mainly reflect the intrinsic repolarization properties and are largely independent of ventricular excitation sequence.^{21,22} Complex multipeak distributions of the QRST integral values have been related to regional disparities of ventricular recovery duration and thus to cardiac states of vulnerability to arrhythmias.^{9,11} However, a multipolar pattern was rarely found in patients affected by long QT syndrome or myocardial infarction with life-threatening ventricular arrhythmias,^{11,13,15} except in 1 series.¹⁰

In the present study the percentage of cases with multipolar QRST integral maps (10%) was small and lower than in our previous series (24%) on a different

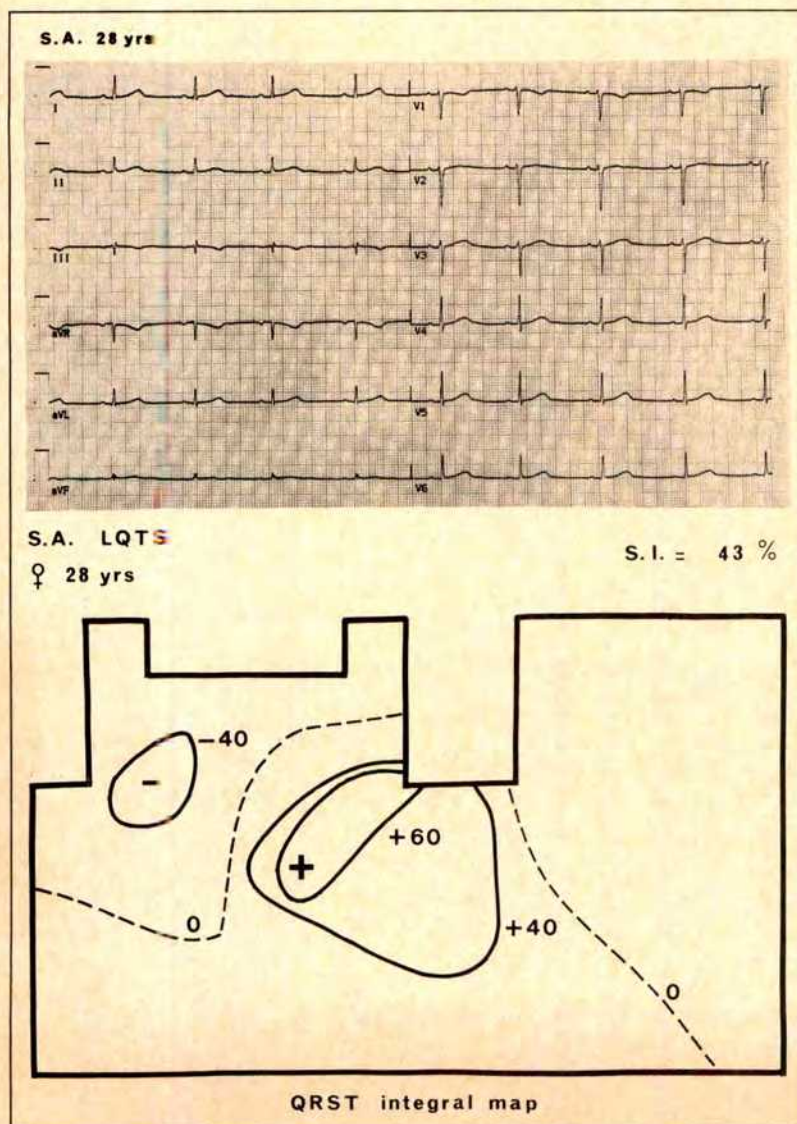


FIGURE 4. Twelve-lead electrocardiogram and QRST integral map from a patient with long QT syndrome (LQTS) (no. 26 in Table I). Distribution of the integral values looks normal (see Figure 3 for comparison); similarity index (S.I.) is definitely low (43%).

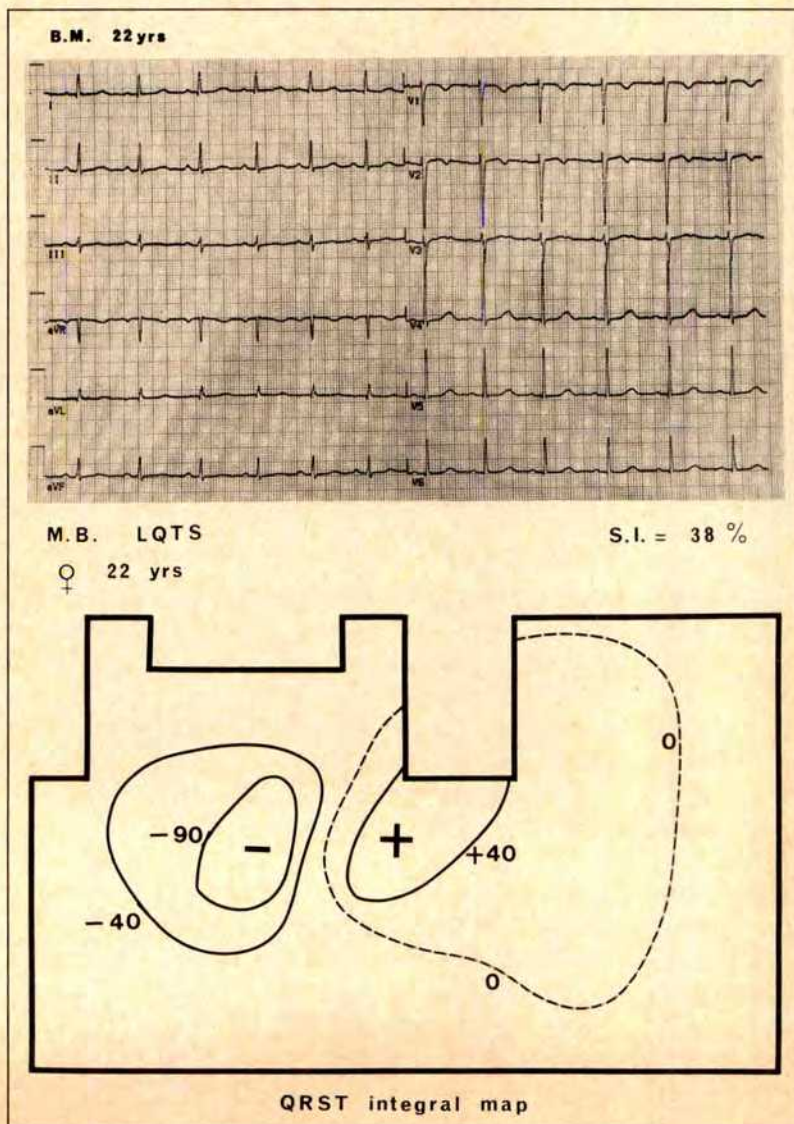
and more limited population.¹⁵ A multipolar distribution most likely reflects only gross regional inequalities of repolarization, and may not represent a marker sufficiently sensitive for minor disparities.

To detect and quantify minor electrical disparities of ventricular recovery times, we analyzed the morphology of all the recorded ST-T waves. We assumed that the more dishomogeneous the ventricular repolarization, the more complex the equivalent cardiac generator, giving rise to a more complex potential distribution at the body surface. On the other hand, the more uniform is the recovery process in the ventricles, the more "dipolar" the surface potential distribution. A smooth dipolar distribution of recovery potentials will result in ST-T waves with very similar shapes although of different amplitude and polarity. This condition will be reflected by a high value in the similarity index. The mean value of the similarity index was significantly lower in patients with long QT syndrome than in control subjects (abnormally low in 87% of the cases).

When the QRST integral maps and the values of similarity index are compared, one notes that all 4 patients with multipolarity had an abnormal value in similarity index, but only in 2 patients was it very low (Table I). However, similar values can be observed in patients with a bipolar distribution of the QRST map (Figure 5). Some patients with long QT syndrome in whom the QRST maps could be considered within normal limits, showed a clearly abnormal similarity index (Figure 4). These findings clearly indicate that the similarity index has a greater capability than QRST integral maps (multipolarity) in detecting electrical dishomogeneities at the body surface, particularly if they occur only during some portions of ventricular repolarization.

Clinical correlates: The value of the similarity index was not correlated with age, sex and heart rate neither in patient with long QT syndrome patients nor in control subjects. Among patients with long QT syndrome, no correlation was found with the type of treatment, or with the severity of the disease. This

FIGURE 5. Twelve-lead electrocardiogram and QRST integral map from a 22-year-old woman affected by long QT syndrome (LQTS) (no. 22 in Table I). Distribution of the values is bipolar, but it is abnormal for the large negativity covering the anterior thorax. Similarity index (S.I.) is 38%.



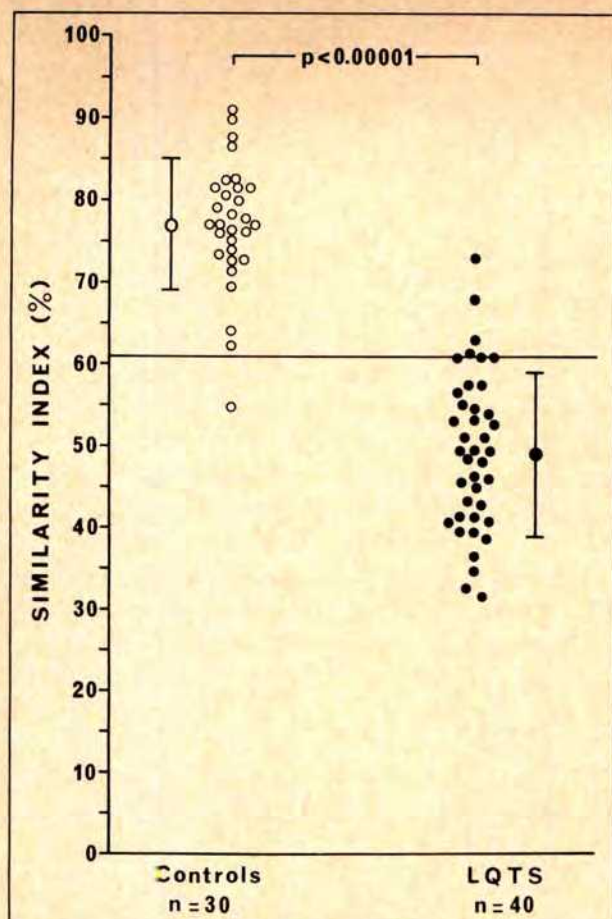


FIGURE 6. Individual values of the similarity index of the control group and the group with long QT syndrome (LQTS). Mean and 1 standard deviation is indicated by a vertical bar for each group. A cutoff value, corresponding to the mean of the control group minus 2 standard deviations, is indicated by the horizontal line.

apparent inability of the similarity index in distinguishing between patients at low or at high risk for syncope matches the weak correlation between QTc and history of syncope/cardiac arrest among patients with long QT syndrome.

Both the multipolar potential distribution and a low similarity index are only markers of 1 specific condition of susceptibility to ventricular arrhythmias; the actual occurrence of arrhythmic events still requires an appropriate trigger, likely to be an increase in cardiac sympathetic activity.^{1,7} This might weaken the relation between the surface electrical signs of repolarization disparities and the occurrence of arrhythmic events.

There was no correlation between QTc and similarity index. Specifically, in 3 patients with normal QTc the similarity index was abnormal (Table I). This suggests that a high degree of disparity of the ventricular recovery times, as indicated by the similarity index, can be equally present both in patients with long QTc and in patients with borderline QTc. Thus, in patients with long QT syndrome, the simi-

larity index provides information complementary to that of the QTc value and can be useful, along with other criteria, for diagnosing borderline or atypical cases.

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Dimensions of the Human Posterior Septal Space and Coronary Sinus

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Accurate anatomic localization of accessory pathways during preoperative electrophysiologic study and during operative mapping depends on a knowledge of the dimensions of the posterior septal space and the left free wall. These dimensions were therefore studied in 48 human cadaver hearts. Mean distance from the coronary sinus orifice to the left margin of the posterior septal space was 2.3 ± 0.4 cm and mean length of the left free wall was 5.0 ± 1.0 cm. The posterior septal space at the level of the valve annuli extended a mean of 3.4 ± 0.5 cm around the epicardium. The width of the posterior septum measured in the coronary sinus was related to heart weight and a combination of body weight and patient age ($p < 0.05$). The probability of an accessory pathway being located in the left free wall or the posterior septum during catheter mapping was calculated for various distances from the coronary sinus orifice for adults of different ages and body weights. In adults, accessory pathways located in the proximal 1.5 cm of the coronary sinus are almost always in the posterior septum. Those located between 1.5 and 3 cm from the coronary sinus orifice may be in either the left free wall or the posterior septum, and those located > 3 cm from the coronary sinus orifice are almost invariably in the left free wall.

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The anatomic localization of accessory pathways is important in determining the approach used for surgical dissection of the atrioventricular junction, thus improving chances of a surgical cure.¹⁻⁸ Pathways in the left free wall are usually dissected using the left atrial endocardial approach described by Sealy and Gallagher.⁷ Pathways in the posterior septum and the right free wall are dissected from either a right atrial endocardial or an epicardial approach, as described by Guiraudon et al.⁹ Surgical division of accessory pathways has a lower success rate when the pathways are located in the posterior septum compared with the atrioventricular free wall.^{1,5,6} The distinction between posterior septal and left free wall accessory pathways is also important for catheter ablation, because location is related to success rates and to the incidence of major complications.¹⁰

During preoperative electrophysiologic study, the electrodes showing earliest activation are correlated with anatomical landmarks using fluoroscopy.^{6,7} At present, the distinction between posterior septal and proximal left free wall pathways depends on the electrophysiologist's judgment, because there are no clear guides or anatomic data locating the point where the posterior septal space becomes the left free wall.^{2,8} This produces less reliable decisions about the surgical approach to be used and causes less accurate information to be given to patients about their chances for surgical cure. Errors in communicating pathway location may also occur owing to different concepts about the dimensions of the posterior septum between electrophysiologists and surgeons, with consequent difficulty in comparing outcomes of various ablative procedures between institutions. In this study we examined 48 cadaver hearts to establish the normal dimensions of the posterior interatrial septal space and the coronary sinus to allow for more accurate prediction of the anatomic location of accessory pathways during electrophysiologic study.

METHODS

All available macroscopically normal fresh adult cadaver hearts were dissected. Patients had a postmortem either for coronial requirements or with the relatives' permission. Patients were excluded if there was evi-

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dence of cardiac failure, hypertrophy or valvular heart disease, or if the coronal pathologist wished to examine the coronary arteries in the posterior interatrial septum in detail.

The heart was transected in a plane parallel to the atrioventricular rings at the level of the coronary sinus (where preoperative recordings are obtained during electrophysiologic study) extending from the atrial epicardium posteriorly to the aorta anteriorly.

Both junctions of the atrial free walls with the posterior septal space were defined, in accordance with published data, as the points at which the atrial endocardium separates from the epicardium to produce the posterior septal space (Figures 1 and 2).^{4,11} This definition results in the posterior interatrial septal space encompassing the area of the heart that can be dissected from a right atrial endocardial approach during surgery.⁴ The central fibrous body was defined as the area of confluence between the aortic, mitral and tricuspid valve anuli, and the membranous ventricular septum (Figure 1).⁷ In this study we defined the length of the coronary sinus as the distance from the coronary sinus orifice to the point where the great cardiac vein enters the anterior interventricular groove, because this is the length that can be readily negotiated with electrode catheters.¹²

Measurements were obtained of various dimensions of the posterior interatrial space (Figure 3). Measurements of the atrial free wall junctions were made at the atrial endocardial surface. Length of the coronary sinus was measured using a flexible catheter inserted in the

coronary sinus extending from the orifice to the origin of the anterior interventricular vein.

Because dimensions vary with age and body size, we developed tables for predicting the width of the posterior interatrial space measured leftward from the coronary sinus orifice, as would be performed during electrophysiologic study.

Although our measurements were obtained with the heart held open under gentle tension, there is a possibility that measurements obtained from the flaccid fresh cadaver heart may not correlate accurately with those of the living heart because of the effects of cardiac dis-

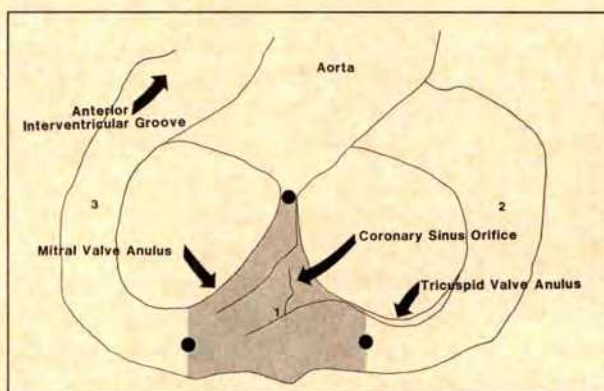


FIGURE 2. Diagram illustrating boundaries of posterior septal space in plane of coronary sinus. Uppermost black pin marks central fibrous body; other black pins mark junctions of left and right free walls with posterior septal space, respectively. Coronary sinus orifice is located at thebesian valve identified by arrow. There is a 1-cm rim of atrial endocardium seen in this diagram (and in Figure 1) located to right of and below coronary sinus orifice. Shaded area, 1, identifies posterior interatrial septum, 2 identifies right free wall and 3 identifies left free wall.

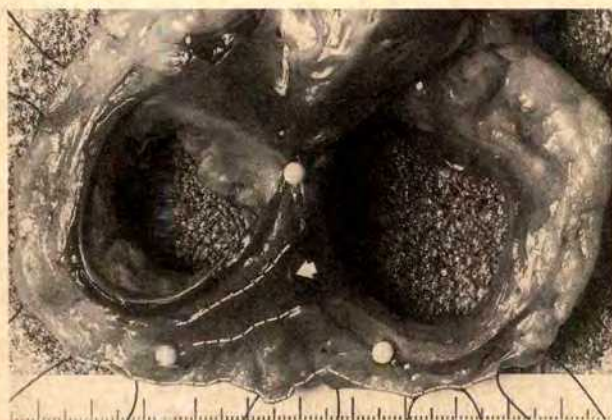


FIGURE 1. Photograph of transverse cardiac dissection at level of coronary sinus. Uppermost white pin indicates central fibrous body; other pins indicate junctions of posterior septal space with left and right free walls, respectively. Arrow points to orifice of coronary sinus and thebesian valve. Anterior dotted white lines mark edges of coronary sinus; posterior dashed white line marks epicardium. Because tricuspid anulus is 1 cm to right of and below coronary sinus orifice, a 1-cm rim of atrial endocardium can be seen between orifice of coronary sinus and tricuspid anulus. Note relatively large size of posterior septal space compared with free walls and dimensions of orifices of atrioventricular valves. Note considerable expanse of posterior septal space posterior to coronary sinus that traverses middle of posterior septal space.

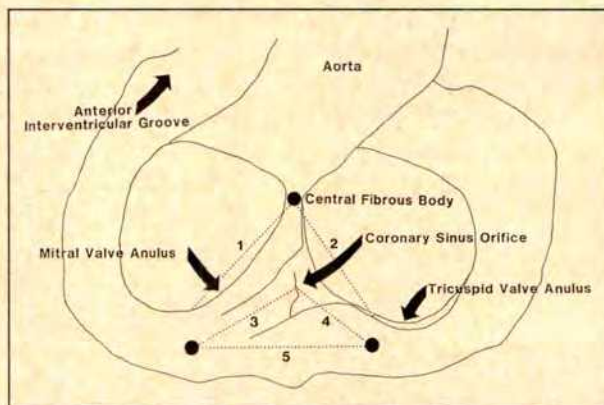


FIGURE 3. Diagram illustrating measurements of posterior septal space. Uppermost black pin marks central fibrous body; other black pins mark junctions of left and right free wall with posterior septal space, respectively. Dotted lines illustrate various measurements obtained in cadaver hearts: 1, central fibrous body to left free wall and posterior septal junction at endocardium; 2, central fibrous body to right free wall and posterior septal junction at endocardium; 3, coronary sinus orifice to left free wall; 4, coronary sinus orifice to right free wall; and 5, left free wall to right free wall junctions with posterior septal space measured at epicardium. Not labeled on diagram but also measured was length of coronary sinus from its orifice to anterior interventricular vein.

TABLE I Various Dimensions of the Posterior Interatrial Septum and the Left Free Wall (cm)

	All Patients		Patients with Normal Hearts		Patients with Coronary Artery Disease		p Value
	n	Mean	n	Mean	n	Mean	
Posterior septum (epicardium)	48	3.4 ± 0.5 (3.5)	41	3.3 ± 0.6 (3.4)	7	3.5 ± 0.3 (3.5)	0.5
Coronary sinus length	48	7.3 ± 1.0 (7.4)	41	7.3 ± 1.0 (7.3)	7	7.4 ± 1.1 (7.5)	0.5
Coronary sinus orifice to left free wall	48	2.3 ± 0.4 (2.3)	41	2.2 ± 0.4 (2.2)	7	2.7 ± 0.3 (2.5)	0.5
Coronary sinus orifice to right free wall	48	1.5 ± 0.3 (1.5)	41	1.5 ± 0.4 (1.5)	7	1.4 ± 0.3 (1.5)	0.5
Central fibrous body to left free wall	48	2.9 ± 0.3 (3.0)	41	2.8 ± 0.3 (3.0)	7	3.0 ± 0.2 (3.0)	0.5
Central fibrous body to right free wall	48	3.0 ± 0.4 (3.0)	40	3.0 ± 0.5 (3.0)	9	3.1 ± 0.4 (3.0)	0.5

Numbers in parentheses = median values.

tension. To examine this, we compared radiographic measurements of the posterior interatrial septum with the heart in varying degrees of distension. This involved initial attachment of radiopaque staples to the epicardium in the posterior atrioventricular groove. The site of attachment was located by palpation at the point where the atrial wall appeared to thicken and become the interatrial septum. The heart was closed by ligation of the great vessels. Intracardiac pressure was monitored in all 4 chambers using Swan-Ganz catheters, 1 portal of which was used for distending the heart with normal saline solution infusion. The separation of the radiopaque markers was measured radiographically at pressures of 0, 16 and 30 cm of water.

Statistical analysis: The data were analyzed using the Statistical Package for Interactive Data Analysis.¹³ Sets of 2 measurements obtained from the same heart were compared using the paired *t* test. Exhaustive searches¹³ were used to determine the best set of 1, 2 or 3 predictors in the multiple regression analyses. Normality of the residuals in the regression models was assessed by plotting the ordered residuals against the expected value of the normal order statistics.¹⁴ The Filliben coefficient was used to test for normality.¹⁴ Fitted regression models were used to predict the probability of the dependent variable lying in a specified range, as described by Weisberg.¹⁵

RESULTS

Forty-eight adult cadaver hearts were examined (34 men and 14 women [average age ± standard deviation 45 ± 19 years, range 15 to 85]). Mean body weight was 66 ± 12 kg, mean height 173 ± 10 cm, mean body surface area 1.78 ± 0.20 m² and mean heart weight 389 ± 67 g.

Death was the result of myocardial infarction in 5 patients, trauma or suicide in 23, pulmonary embolus in 3, infection in 2, cerebrovascular accident in 4, can-

TABLE II Results of Regression Analysis for Predicting the Width of the Posterior Septum Along the Coronary Sinus

	DF	Regression Coefficient	SEM	p Value	r ²
Age (yr)	44	0.005	0.003	0.10	0.06
Height (cm)	46	0.009	0.006	0.15	0.04
Weight (kg)	46	0.013	0.004	0.00	0.16
Body surface area (m ²)	46	0.787	0.282	0.01	0.15
Coronary sinus length (cm)	46	0.130	0.057	0.02	0.11
Heart weight (g)	46	0.003	0.000	0.00	0.20

DF = degrees of freedom; SEM = standard error of the mean.

cer in 2 and ruptured aortic aneurysm in 2. In 1 patient each, death was the result of bleeding, scleroderma, anaphylactic shock and uncontrolled epilepsy. In 3 patients the cause of death was not macroscopically apparent. The heart was normal in 41 patients. In 7 hearts there was evidence of coronary artery disease, including 1 case of a ruptured ventricle due to acute myocardial infarction. No heart showed evidence of cardiac dilation. The absence of cardiac dilation in this latter group reflects the selection bias inherent in examining primarily coroner's cases rather than hospital specimens.

The results of the various measurements of the posterior interatrial septum and coronary sinus are listed in Table I. The coronary sinus orifice to left free wall dimension is the key measurement for preoperative prediction of pathway location in the posterior septum or left free wall. This measurement had a mean of 2.3 ± 0.4 cm (range 1.4–3.0). Length of the left free wall distal to the septal left free wall junction was a mean of 5.0 ± 1.0 cm (range 3.0–6.7). Measurements obtained from patients with ischemic heart disease were no different from those of normal subjects (*p* = 0.5) (Table I).

TABLE III Probability of Location in the Posterior Septum at Various Distances from the Coronary Sinus Orifice in Relation to Body Weight (kg) in a Patient Aged 20 Years

Body weight (kg)							
85	0.99	0.96	0.86	0.66	0.40	0.18	0.06
80	0.99	0.94	0.81	0.58	0.32	0.13	0.04
75	0.98	0.91	0.75	0.49	0.24	0.09	0.02
70	0.96	0.87	0.67	0.40	0.18	0.06	0.01
65	0.94	0.82	0.59	0.32	0.13	0.04	0.01
60	0.91	0.75	0.50	0.25	0.09	0.02	0.00
55	0.87	0.68	0.42	0.19	0.06	0.01	0.00
50	0.82	0.59	0.33	0.14	0.05	0.01	0.00
Distance from coronary sinus orifice (cm)	1.5	1.75	2.0	2.25	2.5	2.75	3.0

TABLE IV Probability of Location in the Posterior Septum at Various Distances from the Coronary Sinus Orifice in Relation to Body Weight (kg) in a Patient Aged 40 Years

Body weight (kg)							
85	1.00	0.98	0.93	0.79	0.56	0.30	0.11
80	1.00	0.97	0.90	0.73	0.47	0.22	0.08
75	0.99	0.96	0.86	0.65	0.38	0.16	0.05
70	0.99	0.94	0.80	0.57	0.30	0.11	0.03
65	0.98	0.91	0.74	0.48	0.22	0.08	0.02
60	0.96	0.86	0.66	0.39	0.16	0.05	0.01
55	0.94	0.81	0.57	0.31	0.12	0.03	0.01
50	0.91	0.74	0.48	0.23	0.08	0.02	0.00
Distance from coronary sinus orifice (cm)	1.5	1.75	2.0	2.25	2.5	2.75	3.0

TABLE V Probability of Location in the Posterior Septum at Various Distances from the Coronary Sinus Orifice in Relation to Body Weight (kg) in a Patient Aged 70 Years

Body weight (kg)							
85	1.00	1.00	0.98	0.91	0.76	0.52	0.27
80	1.00	0.99	0.97	0.88	0.70	0.44	0.21
75	1.00	0.99	0.95	0.83	0.62	0.35	0.15
70	1.00	0.98	0.92	0.78	0.53	0.27	0.10
65	0.99	0.97	0.89	0.71	0.44	0.21	0.07
60	0.99	0.95	0.84	0.63	0.36	0.15	0.04
55	0.98	0.93	0.78	0.54	0.28	0.11	0.03
50	0.97	0.89	0.71	0.45	0.21	0.07	0.02
Distance from coronary sinus orifice (cm)	1.5	1.75	2.0	2.25	2.5	2.75	3.0

Probability tables for predicting width of posterior septal space along coronary sinus in relation to body weight (kg) in other age groups are available on request.

The relations between posterior septal width, measured along the coronary sinus from its orifice, and coronary sinus length, heart weight, age, body height, body weight and body surface area were assessed using simple linear regression. The results are listed in Table II. Heart weight and then body weight were the best single predictors of the posterior septal width along the coronary sinus. Multiple linear regression showed that a combination of age and body weight formed the best model for predicting the width of the posterior septum along the coronary sinus (Table II). We used these results to develop tables listing the probabilities of a pathway being located in the posterior septum based on the

distance from the coronary sinus orifice and the combination of the patient weight and age, because these were the best predictive variables clinically readily available (Tables III to V).

Mean widths of the posterior septum, measured radiographically with the heart distended at 0, 16 and 30 cm of water, were 1.4 ± 0.4 , 1.3 ± 0.4 and 1.4 ± 0.4 cm, respectively. There were no significant differences between these various measurements of posterior septal width.

DISCUSSION

This study provides the only published anatomic data on the width of the posterior septum along the coronary sinus. To date, pathway location has been described as posterior septal rather than left free wall based on soft criteria and the judgment of the electrophysiologist. However, many electrophysiologists and some surgeons do not appreciate the true size of the posterior septal space and incorrectly describe pathways as left free wall when they are actually posterior septal. In these Institutions, posterior septal locations are ascribed to pathways within 1 cm of the os of the coronary sinus rather than up to 2 or 3 times this distance. Frequently, the distinction between the left free wall and the posterior septum is avoided by describing pathways as "paraseptal." However, such equivocal localization is not helpful to the surgeon in choosing an operative approach. Usually the situation is clarified during operative mapping, but accessory pathway function may be temporarily lost during handling of the heart, or tachycardia may not be inducible. In these cases the operation must be based solely on preoperative data. Our data should enable more accurate anatomic location of accessory pathways during electrophysiologic study and surgery, and thereby improve decisions about the route of approach during surgery and communication of the risks and success rates of surgery to the patient. Improved knowledge of the dimensions of the posterior septum should also provide a basis for consensus among electrophysiologists and facilitate more accurate comparison of the outcome and risks of catheter ablation techniques in relation to the anatomic site(s) of the accessory pathway(s).

During electrophysiologic study, the coronary sinus orifice can be localized by observing the point at which the catheter prolapses downward when it is advanced if a superior vena caval approach is used, or by injection of x-ray contrast directly into the coronary sinus or indirectly via the left coronary artery. This provides a reference point for establishing the location of accessory pathways. Subsequent resolution then depends on the spacing of the electrodes. We generally use a 5- or 2-mm interelectrode distance decapolar catheter for adequate resolution in this region.

The results of this study enable the distance of the junction of the posterior septal and the left free wall from the coronary sinus orifice to be estimated with various probabilities based on patient size. Heart weight was the single variable most closely correlated with the dimensions of the posterior septal space, but is not obtainable clinically. The combination of body weight and age was also closely correlated with the dimensions of the posterior septal space and, being easily obtainable, was therefore used to construct probability tables of the likelihood of an accessory pathway being located in the posterior septum at various distances from the coronary sinus orifice. These tables show that the junction of the posterior septum and the left free wall lies >1.75 cm to the left of the coronary sinus orifice in $>75\%$ of all but the smallest adults. Pathways located 3 cm to the left of the coronary sinus orifice are in the left free wall in all but the largest patients.

We could find no detailed published data for comparison with our results. Sealy and Mikat² measured the distance from the central fibrous body to the junction of the left and right free walls with the posterior interatrial septum in 20 patients, but not the width of the posterior septal space along the coronary sinus. They noted considerable variation in their measurements and published only 3 examples to reflect the range of their results. They found values between 15 and 28 mm from the central fibrous body to the left free wall, the lower limit of their range being similar to our own range of 20 to 35 mm. There were no major differences in Sealy and Mikat's measurements of the distance between the central fibrous body and the right free wall (range 20 to 35 mm) and those in this study (range 18 to 40 mm) (Table I).

A potential concern in the application of our results to the living heart relates to possible variation in septal width when the heart is distended by physiologic pressures compared with cadaver hearts held under gentle tension. However, the absence of variation in dimensions of the posterior septal space of cadaver hearts when subjected to various distension pressures up to 30 cm of water suggests that this concern is not important. This absence of variation is probably caused by the area of interest being close to the inelastic fibrous cardiac skeleton that might be expected to remain fairly constant in size during acute pressure changes.

Study limitations: Our data describe adult hearts only and a similar study is required in children.

Probability tables for prediction of posterior atrial septal width were calculated using data from all hearts

studied. It could be argued that the predictive accuracy of these tables would be improved by the elimination of patients with ischemic heart disease who may have some degree of cardiac dilatation. However, no heart in our study showed any evidence of cardiac dilatation or heart failure that may have changed the dimensions of the posterior septum. Table I shows that the measurements made in the 7 hearts with evidence of coronary artery disease were not statistically different from those in the 41 completely normal hearts ($p = 0.5$, Mann-Whitney test). The exclusion of these hearts does not alter the conclusions of this study, but does decrease the number of observations and the accuracy of the tables.

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Stability Over Time of Variables Measuring Heart Rate Variability in Normal Subjects

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Both time and frequency domain measures of heart rate (HR) variability have been used to assess autonomic tone in a variety of clinical conditions. Few studies in normal subjects have been performed to determine the stability of HR variability over time, or the correlation between and within time and frequency domain measures of HR variability. Fourteen normal subjects aged 20 to 55 years were studied with baseline and placebo 24-hour ambulatory electrocardiograms performed 3 to 65 days apart to assess the reproducibility of the following time domain measures of cycle length variability: the standard deviation of all normal cycle intervals; mean normal cycle interval; mean day normal cycle interval; night/day difference in mean normal cycle interval; root-mean-square successive cycle interval difference; percentage of differences between adjacent normal cycle length intervals that are >50 ms computed over the entire 24-hour electrocardiographic recording (proportion of adjacent intervals >50 ms); and the frequency domain measures of high (0.15 to 40 Hz), low (0.003 to 0.15) and total (0.003 to 0.40) power. The mean and standard deviations of these measures were virtually identical between placebo and baseline measurements and within the studied time range. Variables strongly dependent on vagal tone (high-frequency, low-frequency and total power, root-mean-square successive difference, and percentage of differences between ad-

jacent normal cycle intervals >50 ms computed over the entire 24-hour electrocardiographic recording) were highly correlated ($r > 0.8$). It is concluded that measures of HR variability are stable over short periods of time. Certain time and frequency domain variables are highly correlated and may serve as surrogates for each other, and no placebo effect on these variables is evident.

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Heart rate (HR) variability, assessed by both time and frequency domain parameters, decreases with age and with certain disease states such as congestive heart failure, diabetic neuropathy, postmyocardial infarction, and in some forms of inducible ventricular tachycardia or ventricular fibrillation.¹⁻⁴ We have shown that cardiac cycle length variability, the standard deviation of the normal cycles over 24 hours, is a potent univariate predictor of mortality after acute myocardial infarction and remains an independent predictor for mortality even after statistical control for HR, left ventricular ejection fraction, New York Heart Association classification, exercise testing results and ventricular arrhythmias.^{5,6} We have previously shown a strong correlation between time and frequency domain parameters that measure vagal influence. However, there are few data on the reproducibility of repeated measurements.^{7,8} Other variables that predict mortality, such as ventricular arrhythmias or episodes of silent ischemia, vary greatly from one recording to another in any single person.^{9,10}

Fourteen normal subjects underwent 24-hour ambulatory electrocardiograms including baseline and placebo-medicated recordings. No subject took medications; only 1 received a placebo. The questions we addressed were: (1) Is there any placebo effect? (2) How reproducible are the variables that measure heart period variability both in the group as a whole and in individual subjects? (3) How are time and frequency domain measures of heart period variability correlated in normal persons?

Experimental protocol: We obtained two 24-hour Holter recordings in 14 normal subjects, 1 recording

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without treatment (the baseline recording) and the other with a placebo (the placebo recording). The 14 subjects enrolled in the study (10 men, 4 women, aged 25 to 55 years) were normal, healthy volunteers. Each subject supplied a medical history and underwent a physical examination by one of the investigators in order to exclude those with asthma, diabetes, heart disease, hypoglycemia, renal failure or serious systemic disease.

The protocol was approved by the institutional committees on human research at Columbia Presbyterian Medical Center in New York and the Jewish Hospital of St. Louis.

Fourteen patients had placebo and baseline recordings: 7 in <18 days and 7 in ≥ 18 days apart. Four placebo recordings were obtained before the drug-free recordings and 10 afterwards. The intervals between recordings ranged from 3 to 65 days.

Analysis of the twenty-four-hour electrocardiographic recordings: The Holter recordings were analyzed at Columbia University using the Marquette 8000 scanner running version 5.7 of the Marquette arrhythmia analysis program, to identify and label each QRS. The derived data file was reviewed and edited. The review analyzed a frequency histogram of normal cycle intervals and electrocardiograms of the intervals in both tails of the cycle length distribution. The 20 longest and 20 shortest cycle lengths and the cycle with the greatest difference in length was reviewed by a physician. The labeled QRS data stream was moved through a high-speed interface to a Sun 3/160 Microcomputer where the data were analyzed.

Measures of HR variability were calculated and printed for the entire 24 hours and from 7:30 to 21:30 (daytime) and 00:00 to 05:00 (nighttime).^{7,8} One-minute average normal cycle lengths* were calculated for each real-time minute of the 24-hour recordings and maximal and minimal values determined. Each print-out, including electrocardiogram strips showing the largest difference in successive cycles, the largest and smallest normal cycle intervals, and atrial arrhythmias, was reviewed separately by 2 investigators. The time domain measures analyzed for reproducibility included mean normal cycle interval for 24 hours, mean day cycle interval, mean night cycle interval, and mean night/day difference, as well as the cycle length variability (standard deviation of all normal cycle intervals) and the mean and standard deviation of the 5-minute normal cycles.

Analysis of successive normal cycle intervals: Differences between successive cycle intervals provide an index of parasympathetic activity.¹¹⁻¹³ We computed the absolute value of each individual difference between

adjacent cycles and summarized the differences by the percentage >50 ms for the entire 24 hours. Root-mean-square successive difference, a continuous measure of variability appropriate for time series, was calculated using the formula of von Neumann et al.¹⁴

Power spectral analysis of normal cycle intervals:

We computed a HR power spectrum for 5-minute segments of the 24-hour recordings. Annotation data from the Holter system allowed the exclusion of segments with atrial or ventricular premature complexes from the analysis. The remaining 5-minute segments were submitted to subroutines that computed the power spectra of the normal cycles. The methods used for spectral analysis have been described previously.¹⁵⁻¹⁸ A continuous normal cycle interval function was derived from the intervals by filtering and sampling the recordings at 4 Hz. The cycle interval rather than instantaneous HR was analyzed to establish correspondence with the time domain measures used in this study. Bartlett's procedure was used to average fast Fourier transforms of sequential 5-minute segments of the cycle interval function over 24 hours.¹⁸ Power spectra were quantified by the area (power) in 2 frequency bandwidths: 0.04 to 0.15 Hz (low-frequency power) and 0.15 to 0.40 Hz (high-frequency power). The high-frequency power, low frequency power, and total power (power in the band width of 0.003 to 0.40 Hz) were calculated.¹⁷⁻¹⁹

Statistical methods: Total low- and high-frequency power values were log-transformed because the distributions were strongly skewed toward large values. All other variables were analyzed as measured.

A paired *t* test was used to compare baseline measurements to placebo measurements, providing information concerning mean HR variability differences between baseline and placebo recordings. The intraclass correlation coefficient was calculated to measure the strength of the association between baseline and placebo measurements for each variable. This statistic is a measure of intrasubject reproducibility.²⁰ The intraclass correlation coefficient was calculated using results of a 1-way random effect analysis of variance. The standard error of measurement (SEM) (the square root of the error-mean-square from the analysis of variance) was also calculated and has the following uses: (1) If *X* denotes a subject's measured value on 1 variable, and the measurements are normally distributed, and SEM denotes the variable's standard error of measurement, then with 95% confidence the subject's underlying steady-state value lies within the interval $X \pm 0.9$ SEM; and (2) if change is studied, and limits are specified beyond which one may be confident that a real change has occurred, the standard error of the difference between 2 measurements is $SEM \sqrt{2}$ ($1.41 \times SEM$). If one tolerates a 5% risk of falsely declaring a real change (when none has occurred), the required

*A normal cycle length is the RR interval between 2 normal sinus beats.

TABLE I Mean \pm Standard Deviations of Baseline and Placebo Measurements (n = 14)						
Variable	Baseline			Placebo		
	Mean	\pm	SD	Mean	\pm	SD
Average NN interval for 24 hours (ms)	817		99	825		100
Average daytime NN interval (ms)	748		95	761		92
Average nighttime NN interval (ms)	991		128	1,006		130
24-hour standard deviation of NN intervals (ms) (CLV)	166		32	165		38
pNN50 (%)	30		14	27		13
Root-mean-square successive difference (ms)	52		23	52		20
Mean \pm SD of 5-minute NN intervals over 24 hours	81		24	82		23
Night/day difference in average NN interval (ms)	243		84	245		76
Ln total power (0.003–0.40) (ms ²)	8.64		0.51	8.63		0.55
Ln low-frequency power (ms ²)	7.45		0.50	7.43		0.53
Ln high-frequency power (ms ²)	6.67		0.73	6.68		0.70

CLV = cycle length variability; Ln = natural log; NN = normal cycle interval; pNN50 = percentage of differences between adjacent normal cycle intervals > 50 ms computed over the entire 24-hour electrocardiographic recording; SD = standard deviation.

TABLE II Intraclass Correlation Coefficients and Standard Error of Measurement (n = 14)		
Variable	ICC	SEM
Average NN interval for 24 hours (ms)	0.9	33
Average daytime NN interval (ms)	0.9	27
Average nighttime NN interval (ms)	0.7	73
24-hour standard deviation of NN intervals (ms)	0.7	18
pNN50 (%)	0.9	4
Root-mean-square successive difference (ms)	0.9	8
Mean \pm SD of 5-minute intervals over 24 hours	0.9	8
Night/day difference in average NN interval (ms)	0.3	20
Ln total power (ms ²)	0.89	0.18
Ln low-frequency power (ms ²)	0.91	0.16
Ln high-frequency power (ms ²)	0.84	0.28

ICC = intraclass correlation coefficient; SEM = standard error of measurement; other abbreviations as in Table I.

limits are $\pm 196 \times 1.41$ SEM, or approximately ± 3 SEM.

The effect of time between the 2 recordings was also analyzed. The intraclass correlation coefficient between baseline and placebo measurements was calculated for subjects when recordings were obtained within 18 days and compared with subjects in whom the interval between recordings was ≥ 18 days.

RESULTS

Baseline and placebo measurements were obtained for 14 normal subjects. The time between first and second Holter recordings ranged from 3 to 65 days (median 17.5). Mean and standard deviations for baseline and placebo recordings were nearly identical, establishing no placebo effect (Table I).

The intraclass correlation coefficients between the placebo and drug-free recordings are listed in Table II. Correlations were positive for all measures, ranging from a weak correlation of 0.33 for the night/day difference in mean cycle interval to very strong correlation for mean \pm standard deviation of all normal cycle intervals for 5-minute segments of a 24-hour electrocardiographic recording, mean day cycle length, mean cy-

TABLE III Intraclass Correlation Coefficients and Standard Error of Measurement by Time Separating Baseline and Placebo Measurements				
Variable	< 18 Days (n = 7)		≥ 18 Days (n = 7)	
	ICC	SEM	ICC	SEM
Average NN interval for 24 hours (ms)	0.9	25	0.9	39
Average daytime NN interval (ms)	0.9	22	0.9	30
Average nighttime NN interval (ms)	0.7	65	0.6	81
24-hour standard deviation of NN intervals (ms)	0.7	13	0.7	22
pNN50 (%)	0.9	3	0.9	5
Root-mean-square successive difference (ms)	0.9	5	0.9	9
Mean \pm SD of 5-minute NN intervals over 24 hours	1.0	4	0.9	10
Ln total power (ms ²)	0.94	0.10	0.84	0.23
Ln low-frequency power (ms ²)	0.93	0.11	0.88	0.19
Ln high-frequency power (ms ²)	0.90	0.13	0.75	0.35

Abbreviations as in Tables I and II.

cle length, percentage of difference between adjacent normal cycle intervals > 50 ms computed over the entire 24-hour electrocardiographic recording and root-mean-square successive difference. Intraclass correlation coefficients ranged from 0.88 for root-mean-square successive difference to 0.92 for mean day cycle length interval.

Even the night/day difference in average normal cycle interval, which has the lowest intraclass correlation coefficient (in any single individual its measurement could vary greatly from recording to recording), had nearly identical mean and standard deviations for baseline and placebo recordings, demonstrating its usefulness as a measure of HR variability in the group.

Table III presents correlation coefficients between baseline and placebo measurements for variables measured < 18 days or ≥ 18 days apart. All variables were very highly correlated, and the coefficients were essentially the same for those measured < 18 versus those ≥ 18 days apart.

TABLE IV Correlations for 14 Placebo Records

	r-MSSD	pNN50	SDNN	NDDiff	RR	RR.N	RR.D	SDNNIDX
pNN50 (%)	0.96							
24-hour SD of NN intervals (ms) (CLV)	0.78	0.71						
Night/day difference	0.52	0.36	0.78					
Average NN interval for 24 hours (ms)	0.84	0.89	0.80	0.40				
Average nighttime NN interval (ms)	0.87	0.84	0.92	0.72	0.92			
Average daytime NN interval (ms)	0.76	0.88	0.66	0.19	0.97	0.82		
Mean \pm SD of 5-minute NN intervals over 24 hours (SDNN index)	0.97	0.94	0.85	0.53	0.89	0.91	0.85	
Total power	0.94	0.92	0.87	0.57	0.86	0.90	0.85	1.0
Low-frequency power	0.91	0.81	0.85	0.71	0.72	0.86	0.63	0.92
High-frequency power	0.98	0.92	0.68	0.45	0.74	0.77	0.71	0.90
	Total Power		Low Frequency Power					
Low-frequency power	0.93							
High-frequency power	0.88		0.89					

NDDiff = night/day differences; r-MSSD = root-mean-square successive difference; RR = RR interval between normal beats; RR.D = RR interval, day; RR.N = RR interval, night; SDNNIDX = average of the standard deviations of all 5-minute segments over 24 hours; other abbreviations as in Tables I to III.

The relation between time and frequency domain measurements of HR variability for the baseline recordings is shown in Table IV. These findings were essentially duplicated with placebo. Correlations >0.9 were seen between root-mean-square successive difference, percentage of differences between adjacent normal cycle intervals >50 ms computed over the entire 24-hour electrocardiographic recording, and high-frequency power — all measures of vagal tone. Low-frequency power over 24 hours correlated with root-mean-square successive difference (0.9), high-frequency power (0.9), and percentage of differences between adjacent normal cycle intervals >50 ms computed over the entire 24-hour electrocardiographic recording (0.8), clearly showing that 24-hour low-frequency power is also strongly dependent on vagal tone in these normal subjects. Total power over 24 hours also strongly correlated (>0.09) with the aforementioned variables and with high-frequency power and root-mean-square successive differences. On the other hand, cycle length variability had a weaker correlation of only 0.7 with high-frequency power, implying that cycle length variability is influenced by nonvagal factors.

Mean and standard deviations of all normal cycle intervals for all 5-minute segments of a 24-hour electrocardiographic recording index, unlike cycle length variability, showed correlations of ≥ 0.9 for the time domain measures; this reflected vagal tone and all spectral measures, particularly total power, where the correlation was 1.0.

DISCUSSION

There is increasing interest in the evaluation of autonomic tone in a variety of medical conditions, particularly acute and chronic coronary syndromes. Various techniques have been used,^{5,11,21,22} including short-term measurements of respiratory sinus arrhythmia,²³ assessment of baroreceptor sensitivity,¹⁶ HR response to tilt, and long-term ambulatory recording measuring

time domain or frequency domain measures of HR variability.^{1-7,16,17,19,24} Cycle length variability has predicted mortality in a large postinfarction population.⁵ Bigger et al,⁷ in subset analysis of postinfarct patients, demonstrated that low cycle length variability (<50 ms) or high cycle length variability (≥ 100 ms) correlated strongly with other time domain measurements.

Lombardi et al,¹⁹ reported a decrease in high-frequency power and increased low- to high-frequency power ratio in patients after infarct. Bigger et al,¹⁶ in clinical and experimental studies, found that both baroreceptor sensitivity and electrocardiographic-derived measures of HR variability, such as cycle length variability, decrease after infarction, but the correlation of these measurements is not strong. Thus, cycle length variability and other electrocardiographically derived measures of HR variability are not surrogates for baroreceptor sensitivity.

To date, there are few data on these measures in normal subjects. We have shown in the present study that both time and domain frequency measures of HR variability are virtually identical when measured at placebo and baseline intervals. Our data also show that for most of the measured variables, the intraclass correlation coefficient, which is a measure of individual variability, exceeds 0.8. Thus, not only group but also individual measurements are remarkably stable, in contrast to other electrocardiographic-derived variables, such as ventricular premature complexes or episodes of silent ischemia.^{9,10} Because the intraclass correlation coefficients were similar in subjects whose recordings were obtained within 18 days compared with those in which the intervals between recordings were ≥ 18 days, we conclude that these measures are essentially constant during the study range (3 to 65 days).

This study also demonstrates very strong positive correlations between the time domain measures that are vagally mediated. These time domain measures also correlated strongly with high-frequency power, indicat-

ing they can act as surrogates for high-frequency power. This requires validation in other populations, particularly those with coronary artery disease. We also observed that the percentage of differences between adjacent normal cycle intervals >50 ms, computed over the entire 24-hour electrocardiogram recording, root-mean square successive difference and high-frequency power, have very strong positive correlations with total and low-frequency power. Short-term low-frequency power has been shown to be highly dependent on sympathetic tone.^{13,19,21} However, our study demonstrates that low-frequency power calculated over 24 hours is apparently influenced by vagal tone in normal subjects. Cycle length variability, which is influenced by high- and low-frequency powers and also very slow circadian fluctuations, shows considerably weaker correlations with other HR time and frequency domain variables. Thus, these variables cannot be used as surrogates for cycle length variability.

We conclude that HR variables measured in this study are suitable for intervention studies because of their stability over time, lack of placebo effect and marked individual reproducibility. In addition, certain time domain variables can act as surrogates for the frequency domain variables.

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Effectiveness of Imazodan for Treatment of Chronic Congestive Heart Failure

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A 12-week, multicenter, double-blind, randomized, placebo-controlled trial of imazodan, a type III phosphodiesterase inhibitor, was conducted in 147 patients with congestive heart failure to determine clinical efficacy and safety. Patients were randomized to placebo or 2, 5 or 10 mg of imazodan administered twice daily. Patients were maintained on their standard therapy including diuretics, digoxin and an angiotensin-converting enzyme inhibitor. The mean ejection fraction was $23 \pm 10\%$. Exercise time increased from baseline in all 4 groups. There was no significant difference observed between the placebo group and any of the treated groups with regard to exercise time, ejection fraction, frequency of ventricular premature complexes or ventricular tachycardia. When analyzed by intent to treat, the placebo mortality was 7% (3 of 44) and the imazodan mortality was 8% (8 of 103) ($p =$ not significant). This study failed to demonstrate that imazodan provided any benefit in exercise performance when compared with placebo.

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The optimal treatment of congestive heart failure (CHF) remains a major clinical issue despite treatment with digitalis and diuretics. The use of vasodilators,¹ especially the angiotensin-converting enzyme inhibitors,^{2,3} have improved both symptoms and prognosis. Nevertheless, the mortality of patients with advanced CHF remains high and many patients continue to be severely symptomatic despite medical therapy. Type III phosphodiesterase inhibitors may provide an alternative or additional treatment for CHF. These agents have demonstrated hemodynamic efficacy in the acute setting.⁴⁻¹⁰ However, long-term trials studying the effect on exercise performance have generally been disappointing.¹¹⁻¹⁶

Imazodan hydrochloride (CI 914), a selective inhibitor of type III phosphodiesterase, blocks the degradation of cyclic adenosine monophosphate leading to increased intracellular concentrations, thereby increasing myocardial contractility. Imazodan also acts as a peripheral vasodilator in a variety of animal models.¹⁷ Initial human studies⁸ indicated that after intravenous or oral administration of imazodan, cardiac output increases and pulmonary capillary pressure and systemic vascular resistance decrease. Pharmacokinetic studies suggested a half-life of 15 to 25 hours, allowing twice-daily administration.

The primary objective of this study was to determine whether, during a 12-week period, 1 or more dosing regimens of orally administered imazodan were more effective than placebo at increasing exercise time on a treadmill in patients with moderate to severe chronic CHF.

METHODS

Patient population: The study was designed to enroll 160 patients. Recruitment was discontinued after 147 patients were randomized after an analysis of the initial 80 patients indicated that a positive effect of the drug was unlikely to be achieved. Each patient was required to provide written informed consent, be aged >18 and <75 years and have chronic CHF in which dyspnea or fatigue limited their exercise. Patients were allowed to continue receiving antiarrhythmic agents except for disopyramide. Short-acting nitrates and constant doses of digitalis and angiotensin-converting enzyme inhibitors were permitted. Diuretic doses could be decreased, but

TABLE I Baseline Characteristics of Patient Population

	No. of Pts. (n = 147)	Placebo (n = 44)	Imazodan 2 mg BID (n = 34)	Imazodan 5 mg BID (n = 37)	Imazodan 10 mg BID (n = 32)	p Value
Men	128 (87)	39 (89)	32 (94)	30 (81)	27 (84)	0.39
Age	59 ± 9.7	57.5 ± 9.8	59.6 ± 12.2	60.9 ± 7.2	58.3 ± 9.2	0.43
NYHA						0.28
Class III	72 (49)	22 (50)	12 (35)	18 (49)	20 (63)	
Class IV	7 (5)	2 (5)	1 (3)	3 (8)	1 (3)	
Etiology						0.19
CAD	78 (53)	20 (45)	23 (68)	20 (54)	15 (47)	
SH	16 (11)	7 (16)	0 (0)	5 (14)	4 (13)	
IDC	35 (24)	12 (27)	7 (21)	10 (27)	6 (19)	
Other	18 (12)	5 (11)	4 (12)	2 (3)	7 (22)	
Exercise time(s)	506 ± 145	529 ± 152	526 ± 128	462 ± 160	502 ± 127	0.18
Ejection fraction (%)	23 ± 10	24 ± 11	22 ± 7	20 ± 9	25 ± 11	0.18
Holter						
VPCs/hour	153 ± 253	189 ± 270	170 ± 313	106 ± 185	140 ± 228	0.52
24-hour HR	86 ± 12	88 ± 11	85 ± 11	84 ± 13	85 ± 12	0.36
V runs/day	2.3 ± 9.2	4.7 ± 14.1	1 ± 2.5	2.2 ± 9.0	0.5 ± 0.9	0.19
Concurrent medications						
Digitalis	124 (84)	38 (86)	27 (79)	32 (86)	27 (84)	0.83
Lasix dose mg/day	91 ± 67	98 ± 73	86 ± 68	91 ± 61	87 ± 65	0.86
ACE inhibitors	81 (55)	25 (57)	20 (59)	20 (54)	16 (50)	0.90

ACE = angiotensin-converting enzyme inhibitors; BID = twice daily; CAD = coronary artery disease; HR = heart rate; IDC = idiopathic dilated cardiomyopathy; NYHA = New York Heart Association; Other = valvular disease (5), congenital heart disease (3), heart disease not specified (10); SH = systemic hypertension; VPCs = ventricular premature complexes; V runs = ventricular runs > 4 beats at a rate > 100 beats/min.

not increase from that taken during the placebo baseline phase. Women with child-bearing potential were excluded.

Study design: This study was a double-blind, parallel-group comparison of imazodan therapy (2, 5 and 10 mg, administered twice daily) with placebo in patients with chronic CHF. The study began with a 2- to 4-week, single-blind, placebo phase during which routine laboratory and cardiac studies were performed.

During the baseline phase, treadmill exercise tests were performed each week using the Naughton protocol modified by Weber et al.¹⁸ Before randomization, 2 consecutive symptom-limited maximal exercise tolerance tests had to be performed between 4 and 12 minutes and had to be reproducible to within 10%. Patients were then randomly assigned to 1 of the 4 treatment groups and were evaluated every week for 12 weeks. Exercise tests were performed at baseline and at weeks 4, 8 and 12. Ejection fraction was measured by gated radionuclide angiography at baseline and 12 weeks. Twenty-four-hour Holter monitorings were performed at baseline and weeks 1, 4 and 10, and were analyzed at a central site (Cardiodata Inc.). Each tape was analyzed for average 24-hour heart rate, ventricular premature complexes per hour and ventricular runs (>4 beats at a rate >100 beats/min/day).

Patients who withdrew from the study because of lack of efficacy before completing the 12 weeks were eligible to enter an open-label treatment program in

which imazodan could be initiated or increased for symptomatic relief of CHF.

Differences in baseline variables between treatment groups were analyzed by chi-square analysis for discontinuous variable and analysis of variance. Changes in exercise times, ejection fraction, 24-hour heart rate, frequency of ventricular premature complexes and ventricular runs were analyzed by 1 factor analysis of variance using treatment group as the independent factor. A p value <0.05 was considered significant. Definitions from the Cardiac Arrhythmia Pilot Study¹⁹ were used for determining proarrhythmia.

Results were analyzed by intent to treat and also by end point analysis of the last laboratory determinant before the time the double-blind phase was broken because of increased symptoms or death. For the double-blind phase and through 84 days, the relation of the treatment group to survival was examined by estimating survival curves for each treatment using the product-limit method of Kaplan and Meier. The equality of the 4 survival distributions was tested by the log rank (Mantel-Cox) statistic.

Data collection was performed by Parke-Davis Pharmaceutical Research Division. Data were analyzed at the Division of Cardiology, Henry Ford Heart and Vascular Institute with the assistance of the Department of Biostatistics, Henry Ford Hospital.

A safety committee (see Appendix), established before the study initiation, was charged with reviewing

the safety data. The members of the committee were unaware of patient characteristics and had access to the dose of drug each patient was receiving, description of deaths and other adverse events, 24-hour Holter monitor results and clinical laboratory findings.

RESULTS

The baseline characteristics of the 147 patients who entered the study are listed in Table I. The treatment groups were similar with respect to all baseline demographic variables (Table I).

Exercise response: Increases in exercise tolerance were seen in all groups compared with baseline (Figure 1). There was no significant difference between the 4 treatment groups in the change in exercise time from baseline to weeks 4, 8 and 12 (Table II). There was no significant change in ejection fraction between the treatment groups during the study period (Table III).

Of the 146 patients who were classified by New York Heart Association class during both baseline and double-blind phases, 122 (84%) remained in the same class, 12 patients (8%) improved, and 12 were worse. There was no significant difference in class change between the 4 treatment groups ($p = 0.7$).

Arrhythmias: In the imazodan 5- and 10-mg groups, a significant increase in 24-hour average heart rates was observed at 1, 4 and 10 weeks (Table IV).

No significant change occurred in the average frequency of ventricular premature beats per hour (Table V) or runs of ventricular ectopic beats compared with baseline in any treatment group at 1, 4 or 10 weeks. According to the Cardiac Arrhythmia Pilot Study¹⁹ definitions there were 15 patients who had proarrhyth-

TABLE II Change in Exercise Time (seconds) from Baseline

Visit (week)	Placebo	Imazodan (2 mg BID)	Imazodan (5 mg BID)	Imazodan (10 mg BID)	p Value
4	24 ± 108	83 ± 79	75 ± 121	32 ± 123	0.08
8	45 ± 114	65 ± 103	67 ± 127	0 ± 127	0.16
12	48 ± 158	83 ± 129	99 ± 128	52 ± 161	0.58

TABLE III Change in Ejection Fraction (%)

	Placebo	Imazodan (2 mg BID)	Imazodan (5 mg BID)	Imazodan (10 mg BID)
No. of pts.	31	29	28	23
Baseline (%)	26 ± 11	21 ± 8	22 ± 9	25 ± 12
End point (%)	24 ± 11	22 ± 9	22 ± 12	25 ± 14
Difference (%)	-2.4 ± 9.9	0 ± 6.5	0.25 ± 6.9	-0.09 ± 6.7
p Value	0.18	1	0.85	0.95

TABLE IV Change in Average 24-Hour Heart Rate

Week	Placebo	Imazodan (2 mg BID)	Imazodan (5 mg BID)	Imazodan (10 mg BID)	p Value
1	1.5 ± 4.7	0.5 ± 6.0	4.8 ± 7.4	4.8 ± 6.0	<0.005
4	-0.5 ± 6.6	2.0 ± 9.0	4.3 ± 8.8	6.4 ± 7.0	0.005
10	-2.2 ± 6.6	-0.2 ± 6.7	4.3 ± 10.6	6.0 ± 10.3	<0.005

mia on the week 1 Holter. These were distributed evenly through the 4 treatment groups.

Safety: Patient withdrawals during the double-blind phase are listed in Table VI. There was a tendency for greater withdrawal from the placebo group for lack of efficacy than from the imazodan treatment groups. No adverse effects related to imazodan were reported. Investigators reported 7 patients with severe adverse effects requiring withdrawal from the study: These included stomach irritation, resuscitated sudden death,

FIGURE 1. Change in exercise time during the follow-up period in the groups taking placebo and 2.5, 5 or 10 mg of imazodan twice daily. * $p < 0.05$ change from baseline.

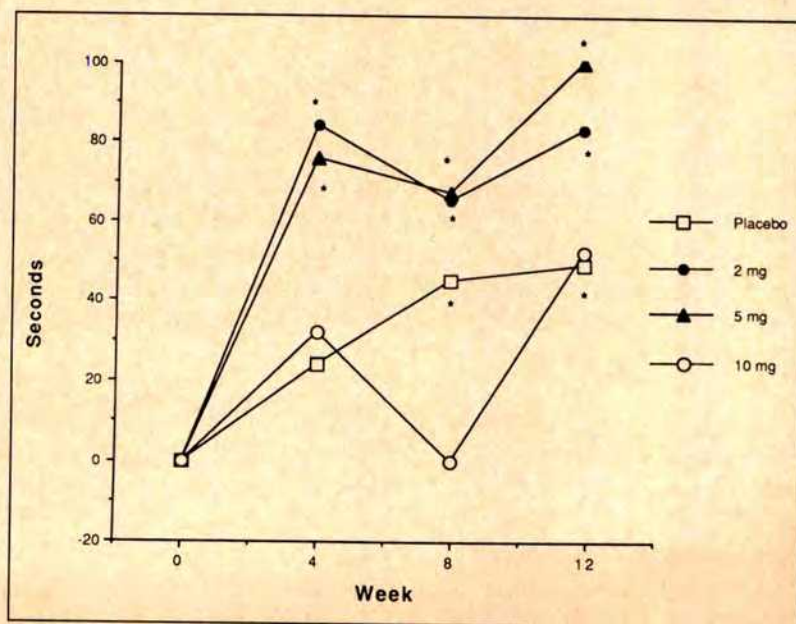


TABLE V Frequency of Ventricular Premature Complexes Per Hour

	Placebo	Imazodan (2 mg BID)	Imazodan (5 mg BID)	Imazodan (10 mg BID)	p Value
Baseline	189 ± 270	170 ± 313	106 ± 185	140 ± 228	0.52
Week 1	190 ± 237	188 ± 327	143 ± 179	109 ± 158	0.49
Week 4	221 ± 287	189 ± 373	163 ± 172	98 ± 114	0.33
Week 10	197 ± 266	167 ± 339	163 ± 253	122 ± 172	0.82

TABLE VI Reasons for Patient Withdrawal During Double-Blind Treatment and Numbers of Patients Completing the 12-Week Period

	Placebo	Imazodan (2 mg BID)	Imazodan (5 mg BID)	Imazodan (10 mg BID)
Death	0	0	4	3
Adverse experience	2	0	3	2
Lack of efficacy	3	1	0	0
Concurrent illness	2	2	0	1
Other withdrawal	6	2	6	4
Completed week 12	32	30	26	22

lightheadedness and headache, nausea, anorexia and weakness, postural dizziness and hypotension, worsening CHF and ventricular arrhythmias.

There were 13 patients with ventricular arrhythmias reported as adverse events by the investigators. Of these, 6 were receiving placebo, 1 was receiving imazodan 2 mg, 4 imazodan 5 mg and 2 imazodan 10 mg twice daily.

By intent-to-treat analysis the mortality in the placebo group was 7% (3 of 44) and in the imazodan groups 8% (8 of 103) ($p =$ not significant). During the double-blind phase of the study there were 7 deaths, 5 of them sudden. Four deaths occurred in the imazodan 5 mg and 3 in the imazodan 10 mg groups. There were 4 additional deaths during the 12-week period in patients who were withdrawn from the double-blind phase. Three were originally in the placebo group and at the time of death 1 of these was taking imazodan 5 mg and another 15 mg twice daily. One was initially in the imazodan 10-mg group, but was withdrawn while hospitalized for CHF and died 11 days later. Patients who died had lower ejection fraction (14 vs 23%, $p < 0.02$), lower baseline exercise times (379 vs 512 seconds, $p < 0.02$), and were less likely to be taking an angiotensin-converting enzyme inhibitor (14 vs 57%, $p < 0.03$).

DISCUSSION

This study examined the efficacy and safety of a new type III phosphodiesterase inhibitor over a range of doses. During the 3 months of follow-up, exercise performance and ejection fraction did not significantly improve when compared with the effect of the placebo.

The drug appeared to be well tolerated. Frequency of ventricular ectopy did not increase, although there was the increase in heart rate seen in the patients taking the larger doses of imazodan. The cause of this chronotropic response has not been previously described and warrants further investigation.

Previous studies with imazodan (CI-914),⁸ its analog CI-930⁹ and other phosphodiesterase inhibitors indicate that intravenous and oral therapy results in an increase in cardiac output and a reduction in peripheral vascular resistance. Although most studies suggest that these drugs have a positive inotropic action, it is difficult, in humans, to separate the effect on contractility from the direct vasodilatation. Patients treated with CI-930⁹ were observed to have an increase in frequency of ventricular ectopy which was not found in this study.

Other phosphodiesterase inhibitors have been evaluated for the treatment of chronic CHF. Amrinone⁴ and milrinone,⁵ both bipyridine derivatives, have significant inotropic and vasodilator effects in the acute setting. The effects of long-term amrinone therapy on exercise performance have been disappointing. Massie et al¹² compared amrinone with placebo in 99 patients with chronic CHF and found no difference in exercise ability over a 12-week period. A multicenter placebo-controlled comparison of milrinone with digoxin¹³ found an improvement in exercise performance in patients given either milrinone or digoxin when compared with placebo, but no additional benefit to the combination of milrinone and digoxin.

Enoximone⁶ and piroximone,⁷ like imazodan, are imidazol derivatives with acute hemodynamic effects similar to amrinone and milrinone. Whereas there have been numerous acute and chronic studies of enoximone²⁰ in patients with heart failure, few have been controlled. Uretsky et al,¹⁶ in a study of 102 patients with chronic CHF, found no improvement in exercise capacity or symptoms compared with placebo.

The design of this study would have permitted an analysis of mortality over 12 weeks although the power was not calculated for studying survival. However, patients who discontinued the double-blind study early were allowed to begin the open-label phase immediately. This resulted in the administration of imazodan, before 84 days, to some patients randomized to placebo.

By intent-to-treat analysis for the 84 days, there was no significant difference in mortality between the placebo group (7%) and those treated with imazodan (8%). The fact that all the deaths that occurred during the double-blind phase were in patients taking large doses of imazodan is disturbing. The effect of phosphodiesterase inhibitors on survival has not been studied in a rigorous manner. Most of the initial hemodynamic studies were conducted in patients with severe heart failure in whom the expected mortality was high. In the few placebo-controlled studies,^{12,13,16} as in this study, there has been a disturbing and consistent trend toward increased mortality in the treatment group. Colucci²¹ reviewed 571 patients enrolled in 3 placebo-controlled studies of milrinone and concluded that there was no evidence for an adverse effect of that drug on mortality. In the largest of these studies, however, there was a trend ($p = 0.08$) toward reduced survival in the milrinone-treated group. The investigators attributed this to a baseline imbalance in ejection fraction which suggested that milrinone was given to a sicker population. After post hoc adjustment of this covariant, the trend toward increased mortality was no longer present. Recently, a mortality study of milrinone in patients with class III and IV heart failure was prematurely terminated because of increased mortality in the milrinone-treated group (Schwartz R, personal communication, Sterling Winthrop, Inc.). Uretsky et al¹⁶ found a higher mortality in enoximone-treated patients than in a placebo-treated group. This increase in mortality was significant when the study was analyzed by double-blind ($p < 0.05$) or intention-to-treat ($p < 0.05$) analyses. In our study, the increased mortality rate was observed in the large dose ranges, suggesting a dose effect.

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APPENDIX

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Comparison of Allografts and Prosthetic Valves When Used for Emergency Aortic Valve Replacement for Active Infective Endocarditis

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Aortic valve replacement (AVR) using allografts is an established method of treating aortic valve disease. It is uncertain, however, whether the increased technical demands of allograft AVR can be justified in emergency operations. This study reports 15 patients treated between 1987 and 1990 for acute bacterial or fungal endocarditis involving the aortic valve. Patients underwent emergency AVR because of severe congestive failure, overwhelming sepsis or cerebral emboli. Eight patients received prosthetic valves (group I: 4 mechanical, 4 porcine) and 7 received human allografts (group II: 5 aortic and 2 pulmonary). The groups were comparable in age (group I, 55 years; group II, 51 years), intravenous drug abuse (group I, 1; group II, 3), and previous AVR (group I, 3; group II, 2). One group I and 4 group II patients had septal abscesses. Additional procedures in group I included mitral valve replacement (2), tricuspid valve replacement (1) and aortic root replacement (1). Additional procedures in group II were mitral valve repair (1), root replacement (1), atrial septal defect closure (1) and aortocoronary bypass (1). Mean bypass times (group I, 189 minutes; group II, 204 minutes) and cross-clamp times (group I, 108 minutes; group II, 121 minutes) were similar. Operative deaths occurred in 4 of 8 group I and 1 of 7 group II patients. All surviving patients have been successfully followed (group I, 28 months; group II, 18 months). No group I patient has required reoperation. One group II patient required reoperation for recurrent infection affecting the allograft, and another group II patient died 10 months postoperatively from noncardiac causes. All other group II patients are alive and well with

functioning allografts. AVR with allografts can be performed safely in this high-risk patient population.

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Orthotopic aortic valve replacement (AVR) using a human valve allograft was first performed by Ross in 1962.¹ Lau et al² and Manhas et al³ extended this operation to the treatment of endocarditis. Since then, several groups have reported their experience with this technique.⁴⁻⁶ Allografts may be the preferred substitute for acutely infected aortic valves because of their resistance to infection.⁷⁻⁸ Despite the successes of allograft AVR for endocarditis, it is likely that most patients requiring emergency operation in this setting are treated with prosthetic valves. It is possible that some surgeons question the appropriateness of performing a more technically demanding procedure on a critically ill patient. In such a patient, the additional time required for proper insertion of an allograft may be thought to compromise the chances for a successful outcome. To evaluate these questions, we have reviewed our results with emergency AVR for endocarditis.

METHODS

Patients: The records of patients undergoing AVR for endocarditis between 1987 and 1990 at 1 institution were reviewed. Patients with valvar disease resulting from previous endocarditis that had resolved by the time of operation, patients treated for an extended period with antibiotics to permit AVR under better conditions, and patients with negative blood and valve cultures at operation were excluded from the study. All patients included in this series required emergency operation for 1 or more clinical criteria: intractable congestive failure, overwhelming sepsis, or documented cerebral emboli attributed to valvar vegetations. Records were examined for preoperative information including demographic data, predisposing factors to endocarditis, bacteriologic findings, and cardiac evaluation by echocardiography and cardiac catheterization. Operative

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TABLE I Patient Data: Allograft Versus Prosthetic Valves for Aortic Valve Replacement for Active Infective Endocarditis

Pt. No.	Age (yr) & Sex	Predisposing Factors	Blood Cultures	Indications for Operation	Operative Findings	Gram Stain of Valve
Group I						
1	77 M	Aortic stenosis	S. aureus	Congestive failure	Vegetations	Not performed
2	69 F	Previous AVR	S. aureus	Congestive failure	Abscess	Gram + cocci
3	47 M	i.v. drug abuse	Str. sanguis	Sepsis	Vegetations	Gram + cocci
4	65 M	Aortic stenosis	Str. bovis	Congestive failure	Vegetations	Not performed
5	47 M	0	Str. hyacis	Congestive failure	Vegetations	Gram + cocci
6	69 F	Previous AVR	S. aureus	Congestive failure	Vegetations	Not performed
7	44 M	Previous AVR	S. aureus	Sepsis	Vegetations	Gram + cocci
8	25 F	i.v. drug abuse	S. aureus	Cerebral embolism	Vegetations	Gram + cocci
Group II						
9	50 F	Aplastic anemia; Hickman catheter	Str. faecalis	Congestive failure	Abscess	Not performed
10	62 M	Previous AVR	C. albicans	Sepsis	Vegetations	Yeast forms
11	59 F	Aortic stenosis	Str. faecalis	Cerebral embolism	Vegetations	Gram + cocci
12	62 F	Atrial septal defect	S. aureus	Cerebral embolism	Abscess Atrial septal defect	Not performed
13	58 F	i.v. drug abuse	Str. faecalis	Congestive failure	Abscess	Gram + cocci
14	24 F	Previous AVR	S. aureus	Congestive failure	Abscess Aorta-RA fistula	Gram + cocci
15	42 M	i.v. drug abuse	S. aureus	Congestive failure	Vegetations	Gram + cocci

AVR = aortic valve replacement; C. = candida; i.v. = intravenous; RA = right atrial; S = staphylococcus; Str. = streptococcus.

TABLE II Operative and Postoperative Data

Pt. No.	Replacement Valve	Bypass Duration (min)	Ischemia Duration (min)	Other Procedures	Operative Result	Long-Term Result
Group I						
1	Porcine	137	100	0	Died	—
2	Porcine	220	145	0	Died	—
3	Porcine	109	60	0	Survived	Alive and well 25 mo. po
4	Mechanical	116	71	0	Survived	Alive and well 26 mo. po
5	Mechanical	211	156	Mitral valve replacement	Survived	Alive and well 26 mo. po
6	Mechanical	358	93	Aortic root replacement	Died	—
7	Mechanical	227	158	Mitral valve replacement	Survived	Alive and well 34 mo. po
8	Porcine	130	83	Tricuspid valve replacement	Died	—
Group II						
9	Allograft PV	277	114	Mitral valve repair	Survived	Alive and well 21 mo. po
10	Allograft AV	216	135	0	Died	—
11	Allograft PV	190	137	Aortocoronary bypass X2	Survived	Alive and well 8 mo. po
12	Allograft AV	164	120	Atrial septal defect closure	Survived	Alive and well 13 mo. po
13	Allograft AV	214	125	0	Survived	Alive; late repeat AVR 24 mo. po
14	Allograft AV	228	127	Aortic root replacement	Survived	Died 10 mo. po of noncardiac causes
15	Allograft AV	140	87	0	Survived	Alive and well 18 mo. po

AV = aortic valve; AVR = aortic valve replacement, po = postoperatively; PV = pulmonary valve.

findings, techniques and results were noted. Pathologic and bacteriologic analyses of operative specimens were reviewed.

The choice of valve substitute was made by the surgeon before beginning the operation. The decision to use or not to use an allograft valve was based on the surgeon's experience with and confidence in these materials, and did not reflect any other patient selection factors such as age, cardiac function, hemodynamic instability or associated procedures required. In only 1 case was this decision altered. One patient for whom an

allograft was intended had an aortic anulus that exceeded the size of any available allograft. This patient therefore received a porcine valve. For patients in whom an allograft valve was selected, an aortic valve allograft was used when possible. When no aortic allograft was available in the correct size, a pulmonary valve allograft was used instead. Mechanical or bioprosthetic valves were selected in non-allograft recipients based on criteria such as patient age, contraindications to anticoagulation, possible desire for pregnancy, and ability to comply with a medical regimen. Antibiot-

ic coverage was instituted at diagnosis and continued for 6 weeks postoperatively. Postoperative data were obtained by outpatient follow-up in our clinic, or by phone with the patient and the patient's personal physician. No patient was lost to follow-up.

RESULTS

Of 15 patients who met the criteria for emergency AVR for endocarditis, 12 underwent operation within 24 hours of diagnosis, all within 48 hours. Eleven patients were taken to the operating room immediately after cardiac catheterization, echocardiography or computerized tomography. Data are summarized in Tables I and II. Eight patients (group I) underwent AVR with a prosthetic valve (4 mechanical, 4 bioprosthetic valves) and 7 patients (group II) underwent AVR with a cryopreserved human aortic valve (5) or pulmonic valve (2).

Group I included 5 men and 3 women and group II included 2 men and 5 women. Groups I and II were similar in mean age (group I, 55 years; group II, 51 years), frequency of intravenous drug abuse (group I, 1 patient; group II, 3 patients), and history of previous AVR with a prosthetic valve (group I, 3 patients; group II, 2 patients). A comparison of patients with native valve endocarditis to those with prosthetic valve endocarditis is listed in Table III. Cardiopulmonary bypass times were significantly longer in patients with prosthetic valve endocarditis, but no other statistically significant differences were found. Additional operative findings were septal abscess in 1 group I and 4 group II patients, mitral valve endocarditis in 1 group I and 1 group II patient, atrial septal defect in 1 group II patient, and aorta-right atrium fistula in 1 group II patient. All patients had positive blood cultures at the time of operation. Cultures of valvar vegetations or blood, or both, in group I patients were positive for *Staphylococcus aureus* in 5 patients, and for *Streptococcus sanguis*, *Streptococcus bovis*, and *Streptococcus hyacis* in 1 patient each. Cultures in group II patients were positive for *Staphylococcus aureus* in 3 patients, *Streptococcus faecalis* in 3, and *Candida albicans* in 1. All staphylococcal species were sensitive to methicillin.

Additional procedures performed in group I patients included replacement of the mitral valve (2), tricuspid valve (1) and aortic root (1). Additional procedures in group II were mitral valve repair (1), aortic root replacement (1), atrial septal defect closure (1) and coronary artery bypass $\times 2$ (1). Mean duration of cardiopulmonary bypass (group I, 189 minutes; group II, 204 minutes) and aortic cross-clamping (group I, 108 minutes; group II, 121 minutes) were not significantly different.

Perioperative deaths occurred in 4 of 8 group I patients and in 1 of 7 group II patients. Three group II patients with septal abscesses required insertion of per-

TABLE III Comparison of Patients Undergoing Operation for Native Versus Prosthetic Valve Infections

	Native Valve Infection	Prosthetic Valve Infection
Number of patients	10	5
Age (years)	53 \pm 4	54 \pm 8
Indications for operation		
Congestive failure	6	3
Sepsis	1	2
Cerebral emboli	3	0
Patients requiring additional procedures	5	3
Cardiopulmonary bypass duration (min)	169 \pm 17	250 \pm 24*
Cardiac ischemic duration (min)	105 \pm 10	132 \pm 10
Operative results		
Survived	8	2
Died	2	3
Long-term results		
Well without reoperation	7	1
Well after reoperation	1	0
Late death	0	1

*p = 0.02. Values are mean \pm standard error of the mean.

manent pacemakers for complete heart block. Two had documented heart block preoperatively. No other significant complications were encountered. All patients with focal neurologic injury attributed to preoperative emboli exhibited improvement after AVR, and no new neurologic problems were encountered.

Mean duration of follow-up has been 28 months in group I and 18 months in group II. One group II patient, who continued to use intravenous drugs, developed recurrent endocarditis 6 months after allograft AVR. This patient was successfully treated medically, and cardiac catheterization demonstrated competence of her allograft valve. She presented to another hospital 18 months after allograft AVR with severe aortic insufficiency. At reoperation, she was found to have a perforation of 1 valve leaflet. Blood and valve cultures at operation were negative. Her allograft was replaced with a porcine valve in accordance with the preference of the surgeon treating her at that time. One group II patient died in a motor vehicle accident 10 months after AVR. All other group I and II patients are alive and well, without evidence of valve dysfunction.

DISCUSSION

The frequency of endocarditis may be increasing, perhaps due to nosocomial infections resulting from invasive procedures, immunosuppressed states and intravenous drug abuse, among other factors. In addition, a substantial percentage of all endocarditis is encountered among patients with previously inserted prosthetic valves. The bacteriologic characteristics of endocarditis are changing as well. Although the frequency of *Streptococcus viridans* endocarditis appears to be decreasing, this may actually reflect an increasing frequency of other organisms.⁹ Thus, the need for operative intervention will likely increase as well. Most patients with endocar-

ditis are best treated nonoperatively unless there is a specific indication for operation. However, endocarditis associated with severe aortic insufficiency and congestive failure is fatal in 40 to 93% of patients without surgical treatment.⁹ Endocarditis with septic emboli, overwhelming sepsis, intracardiac abscess, conduction disturbance, resistant organisms, suppurative pericarditis or clinical deterioration despite appropriate antibiotics are other indications for AVR.

When operation is indicated for endocarditis, it is preferred that antibiotics be used to control the infection, so that valve replacement may have the highest probability of success.^{10,11} However, inappropriate delay to achieve bacteriologic "cure" may carry excessive risk.¹² The operative mortality of valve replacement for active endocarditis is 3 to 4 times that for controlled infection.^{11,12} The patients in this series represent the extreme portion of the endocarditis spectrum. All of these patients required emergency operation because of specific clinical findings (hemodynamic collapse, cerebral emboli or septic shock) that were contraindications to even a brief trial of nonoperative therapy. Reports of surgical intervention for active endocarditis often have included patients who underwent operation after lengthy antibiotic therapy¹⁴ as well as patients with moderate congestive heart failure as an indication for operation.¹³ Nevertheless, reported operative mortality for valve replacement for endocarditis has been as high as 30%.^{11,13-16}

Comparison of published series is made difficult by the wide differences in definitions. "Early" operations for endocarditis have included patients treated for 1 week to 2 months after diagnosis.¹⁷⁻¹⁹ Most series describing emergency valve replacement for endocarditis report high frequencies of death and early reoperations.^{13,20,21} However, there are reports of patients undergoing emergency valve replacement for endocarditis with survival of $\geq 90\%$.^{22,23}

In such an emergency setting, the selection of valve replacement may be influenced by perceived difficulties related to the patient's condition and to technical problems. Considerations of long-term valve function, hemodynamic performance, resistance to reinfection and freedom from anticoagulant therapy may be subordinate to accomplishing an expeditious procedure and improving the patient's chances of operative survival. Although allografts are more resistant to infection, use of allografts requires greater ischemic time and more precise operative technique. As a result, the use of aortic valve allografts for AVR may be questioned.

The results of this series suggest allografts are acceptable replacements even in the most seriously ill patients with endocarditis. Bypass and ischemic times were not significantly greater in allograft recipients. Long-term results of allograft AVR in this setting re-

main unknown, although our only patient requiring late reoperation continued to use intravenous drugs after her AVR. The 1 operative death among allograft recipients occurred in a patient with fungal infection of a prosthetic valve, a condition that is fatal in 80 to 90% of cases.^{24,25}

AVR for endocarditis was first described in 1965.²⁶ Allograft AVR for endocarditis was first reported in 1970.³ In 1984, Ross's group described aortic root replacement with an allograft for prosthetic valve endocarditis.² Since then, others have established the efficacy of allografts for both freehand AVR and aortic root replacement in endocarditis.⁴⁻⁶ The advantages of allografts in patients with endocarditis include resistance to reinfection, easier management of root abscesses, and success in severe endocarditis where prosthetic valves have failed.²⁷ These advantages are amplified by the excellent performance of allografts with respect to hemodynamics, durability and freedom from thromboembolism. Long-term follow-up after valve replacement for active endocarditis is important. The 5-year survival in these patients is 40 to 79%, with a reoperation rate as high as 13%.^{16,19,28} Allografts may improve these long-term results. The use of pulmonary valve allografts for AVR has rarely been reported.²⁹ Pulmonary allografts require more precise technique because they are less rigid, and their long-term durability is uncertain. However, pulmonary allografts may calcify less than aortic allografts.³⁰

In treating endocarditis surgically, the replacement material used is only one factor affecting the results. Prompt intervention, adequate debridement, obliteration of fistulas, resection of mycotic aneurysms, secure suture placement and antibiotic treatment are unquestionably of greater importance. The operative outcome is also heavily dependent on the patient's underlying condition and left ventricular function. We believe the results of this study support the use of allografts for emergency AVR for endocarditis. Further use and more long-term follow-up are needed to fully evaluate the benefits of this approach.

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Electrocardiographic Correlates with Left Ventricular Morphology in Idiopathic Dilated Cardiomyopathy

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The purpose of the present study was to verify whether the electrocardiographic pattern of patients with idiopathic dilated cardiomyopathy (IDC) might be useful in predicting measurements of left ventricular (LV) morphology. A total of 12 electrocardiographic criteria for LV enlargement were evaluated in 67 patients with IDC, aged 14 to 68 years (mean 48), and were correlated to LV wall thickness, volume and mass, as assessed at angiography (all patients) and echocardiography (50 patients). Linear regression analysis showed weak correlations between multiple electrocardiographic criteria and LV wall thickness, volume and mass. Multiple logistic regression analysis showed that total 12-lead QRS amplitude, voltage criteria of Sokolow and Lyon, overshoot and U-wave inversion were the variables significantly related to LV wall thickness, as assessed by angiography ($r = 0.55$, $p < 0.005$) and echocardiography ($r = 0.43$, $p < 0.025$). The sum of T/R-wave ratios, the RV_6/RV_5 ratio and the Romhilt-Estes score were predictors of LV end-diastolic volume, as determined by angiography ($r = 0.83$, $p < 0.001$) and echocardiography ($r = 0.77$, $p < 0.005$). Total 12-lead QRS amplitude and the sum of T/R-wave ratios were the only independent predictors of LV mass, either angiographically ($r = 0.81$, $p < 0.001$) or echocardiographically measured ($r = 0.71$, $p < 0.025$). It is concluded that a single electrocardiographic criterion for prediction of LV morphology in patients with IDC is barely effective. Multiple electrocardiographic criteria should be utilized to better predict LV mass and distinguish reliably between LV wall thickening and dilatation.

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Idiopathic dilated cardiomyopathy (IDC) is characterized by an increased left ventricular (LV) mass, as a consequence of LV dilatation and hypertrophy. Several investigations have been performed to identify electrocardiographic predictors of LV morphology in patients with IDC,¹⁻⁶ but controversy persists about the reliability of the electrocardiogram as a means of identifying different patterns of LV anatomy in cardiac patients.^{7,8} To verify whether the electrocardiographic pattern can predict LV mass in patients with IDC, 12-lead electrocardiograms from 67 patients with IDC were analyzed, and compared with angiographic and echocardiographic data. A further object of the study was to investigate whether LV wall thickening can be reliably distinguished from LV dilatation on the basis of the electrocardiographic criteria. A multivariate model was applied to strengthen the relation between electrocardiographic criteria and LV measurements.

METHODS

Patient group: The study included 67 patients (53 men and 14 women, mean age \pm standard deviation 48 ± 11 years [range 14 to 68]) admitted from January 1977 to December 1988. In all patients, 12-lead electrocardiograms and data from cardiac catheterization, including left ventriculography, could be reviewed. Echocardiographic images were available from 55 patients (82%) referred since 1980. The diagnosis of IDC was made on the basis of LV dilatation and systolic contraction dysfunction, as shown by LV ejection fraction $< 50\%$ and LV end-diastolic pressure > 12 mm Hg, in the absence of coronary artery disease, systemic hypertension, cor pulmonale, previous infectious disease, chronic systemic disease involving the heart muscle and increased alcohol intake.

Electrocardiography and terminology: Standard 12-lead electrocardiograms were recorded as $25 \text{ mm} \cdot \text{s}^{-1}$ and $1 \text{ mV} \cdot \text{cm}^{-1}$ standardization.⁹ In all patients, the electrocardiograms were recorded 1 week before cardiac catheterization. All tracings were analyzed by 2 investigators (CC and FP) independently, without knowledge of other patient data. Discrepancies in interpretation were resolved by consensus opinion. A total of

12 electrocardiographic criteria for LV enlargement were evaluated. Amplitude measurements were obtained from 5 consecutive complexes to minimize possible beat-to-beat variation due to respiration. Values were then averaged from the measured beats in every lead. For each lead, R-wave and T-wave amplitudes were measured from the PR segment to the peaks of R and T waves, respectively. The ratio of T to R wave was then determined. The amplitude of QRS waves, defined as the number of millimeters between the point of maximal inflection (top of the R wave) and deflection (bottom of the Q or S wave, whichever was greater), was measured for each lead according to Siegel and Roberts.¹⁰ Sum of R waves, sum of T waves, sum of the T/R-wave ratios, as well as total 12-lead QRS amplitude were obtained by adding the amplitudes of the individual leads. The transverse/frontal plane QRS voltage ratio was calculated as proposed by Goldberger et al³; frontal plane QRS voltage was computed as the sum of peak-to-trough QRS amplitudes in the 2 limb leads with highest QRS voltage, and transverse plane QRS voltage as the maximal peak-to-trough QRS voltage in leads (V₁ or V₂) + (V₅ or V₆). According to Spodick and Koito,⁴ the RV₆/RV₅ ratio was defined as the ratio of R-wave voltages between leads V₆ and V₅. Calculation of the Cornell voltage criteria was based on the sum of the R voltage in aVL and the S-wave voltage in V₃.⁶ QRS duration, the Sokolow and Lyon precordial voltage¹¹ as well as the point score system of Romhilt and Estes,¹² were also measured. Patients showing an inverted T-wave and terminal T-wave positivity in 1 or more leads were defined as having an "overshoot."¹³ U-wave inversion was considered present if a discrete negative deflection was detected within the TP segment in the leads in which the U wave is positive in normal subjects.¹⁴

Cardiac catheterization: Right- and left-sided cardiac catheterization were performed with the patient in the fasting state without premedication. Endocavitary pressures were measured before angiocardiography through a no. 7Fr or 8Fr end-hole catheter placed in the cardiac chambers by the femoral technique. LV end-diastolic and end-systolic volumes as well as ejection fraction were calculated from the 30° right anterior or oblique projection of the left ventriculogram according to Kennedy's area-length method.¹⁵ LV wall thickness and mass were derived according to Dodge's method.¹⁶ All values were corrected to body surface area. Patients with significant angina and those aged ≥30 years also underwent selective coronary arteriography: none had significant stenoses of epicardial coronary vessels.

Echocardiography: Echocardiographic data were available from 55 patients (82%), but M-mode echocardiographic recordings were considered technically

TABLE 1 Values of 10 Parametric Electrocardiographic Criteria for Determining Left Ventricular Morphology as Assessed in 67 Patients with Idiopathic Dilated Cardiomyopathy

Electrocardiographic Criteria	Mean ± SD	Range
Sum of R waves (mm)	59 ± 25	17–138
Sum of T waves (mm)	32 ± 18	7–86
Sum of T/R-wave ratios	17 ± 15	1–67
Total QRS amplitudes (mm)	153 ± 49	52–300
Transverse/frontal plane		
QRS voltage ratio	2.4 ± 0.9	1–5.2
RV ₆ /RV ₅ ratio	1.3 ± 1.2	0.5–9
Sokolow and Lyon index (mm)	37 ± 12	12–75
Cornell voltage criteria (mm)	28 ± 11	11–64
Romhilt-Estes score (n)	4.1 ± 2.3	0–9
QRS duration (ms)	108 ± 25	80–160

SD = standard deviation.

satisfactory in 50 (75%). Measurements were obtained according to the recommendations of the American Society of Echocardiography with a leading-edge-to-leading-edge convention.¹⁷ Standard echocardiographic values of LV internal dimension (LVID), interventricular septum (IVS), and LV posterior wall thickness (PWT) were assessed. LV mass (LVM) was calculated according to "Penn" criteria and formula of Devereux and Reichek¹⁸: LVM (in grams) = 1.04 (LVID + PWT + IVS)³ – (LVID)³ – 13.6 g. LV volume (LVV) was calculated according to Teichholz et al¹⁹: LVV (in milliliters) = 7 (LVID)³/2.4 + LVID. Values were indexed by the body surface area.²⁰

Statistical analysis: Results are expressed as mean ± standard deviation (SD). Angiographically and echocardiographically assessed measurements of LV morphology were compared by means of the paired *t* test. In addition, correlations between morphologic data were tested using linear regression coefficients.²¹ Simple linear regression analysis was also used to evaluate the relation of electrocardiographic criteria to LV morphologic data. A model of logistic regression was then chosen for multivariate analysis.²² This method allows prediction in the likelihood of an event, i.e. the value of LV morphologic parameter in the present study, from measurements of continuous variables. The electrocardiographic variables were included stepwise in order of decreasing *p* values (linear regression analysis). When the addition of a variable did not improve the fit of the model, the variable was omitted. This was the case, for instance, when 2 variables included in the model were related to each other. Each multiple correlation coefficient was determined by a combination of electrocardiographic variables as a function, respectively, of LV myocardium thickness, LV end-diastolic volume, and LV mass. To test the accuracy of the multivariate model, the technique of cross validation was applied.²³ Statistical tables were used to determine the statistical significance of results.²¹ A value *p* < 0.05 was considered statistically significant.

TABLE II Correlations of Electrocardiographic Variables with Angiographically and Echocardiographically Assessed Measurements of Left Ventricular Morphology as Revealed by Simple Linear Regression Analysis

	LV Wall Thickness				LV End-Diastolic Volume				LV Mass			
	Angiography (n = 67)		Echocardiography (n = 50)		Angiography (n = 67)		Echocardiography (n = 50)		Angiography (n = 67)		Echocardiography (n = 50)	
	r	(SE)	r	(SE)	r	(SE)	r	(SE)	r	(SE)	r	(SE)
Sum of R waves	0.09	(1.9)	0.23	(1.9)	0.16	(86)	0.12	(88)	0.02	(75)	0.10	(73)
Sum of T waves	0.23	(1.7)	0.19	(1.9)	0.34*	(82)	0.36†	(82)	0.29†	(71)	0.36*	(68)
Sum of T/R-wave ratios	0.19	(1.8)	0.18	(1.9)	0.47†	(76)	0.45*	(77)	0.53†	(54)	0.45*	(62)
Total QRS amplitudes	0.47*	(1.4)	0.40†	(1.6)	0.21	(83)	0.19	(87)	0.55†	(52)	0.51†	(56)
Transverse/frontal plane												
QRS voltage ratio	0.29	(1.7)	0.05	(2.0)	0.37*	(81)	0.33†	(86)	0.20	(74)	0.18	(72)
RV ₆ /RV ₅ ratio	0.10	(1.8)	0.08	(1.9)	0.43†	(78)	0.41*	(80)	0.23	(73)	0.08	(75)
Sokolow and Lyon index	0.45*	(1.6)	0.39†	(1.7)	0.21	(83)	0.27	(85)	0.25†	(72)	0.28†	(70)
Cornell voltage criteria	0.19	(1.8)	0.06	(1.9)	0.38*	(81)	0.37*	(84)	0.23	(73)	0.10	(73)
Romhilt-Estes score	0.21	(1.7)	0.04	(2.0)	0.39*	(80)	0.42*	(79)	0.11	(74)	0.21	(71)
QRS duration	0.15	(1.8)	0.11	(1.9)	0.29†	(83)	0.38*	(84)	0.20	(73)	0.22	(71)

*p < 0.01; †p < 0.05; ‡p < 0.001.

LV = left ventricular; r = correlation coefficient; SE = standard error of the estimate.

RESULTS

Presenting features: Data at diagnosis from both echocardiography and left ventriculography could be evaluated in 50 patients (75%). Statistical analysis did not show any significant difference between angiographically and echocardiographically determined values of LV wall thickness (mean value \pm SD, 8.5 ± 1.8

mm [range 5 to 13] vs 9.0 ± 1.9 mm [range 5 to 14], respectively, p = not significant [NS]; correlation coefficient = 0.68, p < 0.001), LV end-diastolic volume (mean value \pm SD, 202 ± 86 ml·m⁻² [range 93 to 431] vs 220 ± 101 ml·m⁻² [range 88 to 415], respectively, p = NS; correlation coefficient = 0.73, p < 0.0001), and LV mass (mean value \pm SD, 158 ± 73 g·m⁻² [range 65 to 375] vs 160 ± 71 g·m⁻² [range 60 to 353], respectively, p = NS; correlation coefficient = 0.87, p < 0.0001). Table I depicts mean value \pm SD and range of electrocardiographic variables as assessed in the whole study population. Overshoot was detected in 20 patients (30%), and U-wave inversion was present in 7 (10%).

Linear regression analysis: Table II shows the relation of electrocardiographic criteria to both angiographically and echocardiographically assessed measurements of LV morphology. Linear regression analysis showed a significant, positive correlation of LV wall thickness with total 12-lead QRS amplitude and Sokolow and Lyon index. In contrast, LV end-diastolic volume related significantly to the sum of T waves, sum of T/R-wave ratios, transverse/frontal plane QRS voltage ratio, Cornell voltage criteria, RV₆/RV₅ ratio, Romhilt-Estes score and QRS duration. Also, there was a significant correlation between LV mass and total 12-lead QRS amplitude (Figure 1), sum of T/R-wave ratios (Figure 2), sum of T waves, and Sokolow and Lyon index.

Multiple logistic regression analysis: Total 12-lead QRS amplitude and voltage criteria of Sokolow and Lyon were the first 2 variables selected for prediction of increased LV wall thickness. Overshoot and U-wave inversion were additional variables that significantly improved the fit of the model. The regression coefficients of the final models were 0.55 (F value = 5.45, p

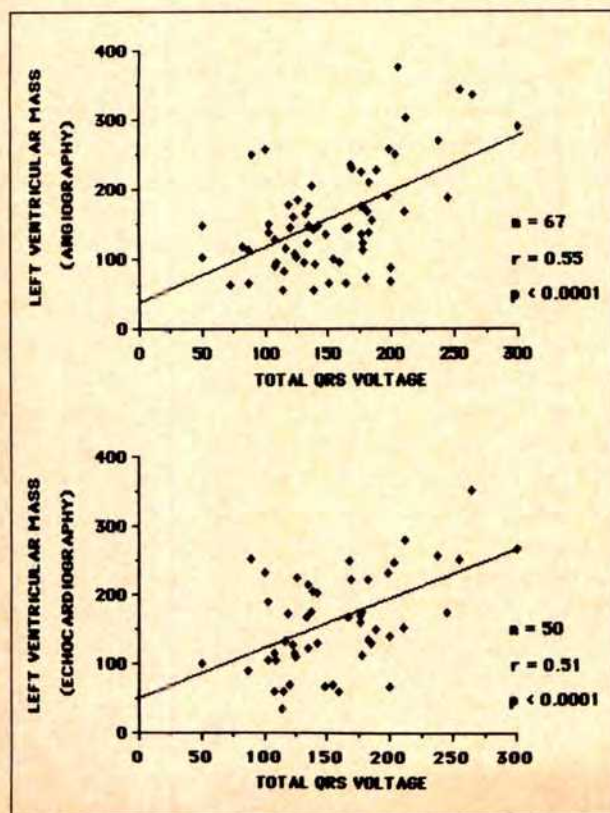


FIGURE 1. The relation between total 12-lead QRS amplitude and left ventricular mass as assessed either at angiography (upper panel) or at echocardiography (lower panel) in patients with idiopathic dilated cardiomyopathy.

<0.005) for angiographically derived LV wall thickness and 0.43 (F value = 4.05, $p < 0.025$) for the echocardiographically assessed one. The sum of T/R-wave ratios, the RV_6/RV_5 ratio and the Romhilt-Estes score were the strongest independent predictors of an increased LV end-diastolic volume, as determined by angiography ($r = 0.83$, F value = 14.45, $p < 0.001$) or echocardiography ($r = 0.77$; F value = 6.29, $p < 0.005$). Electrocardiographic variables were then included stepwise to assess their relation to LV mass. Only total 12-lead QRS amplitude (Figure 1) and the sum of T/R-wave ratios (Figure 2) entered the equation. Statistical analysis showed that these criteria were independent of each other. No additional variable could substantially improve the fit of the model. The multivariate equations showed correlation coefficients of 0.81 (F value = 19.15, $p < 0.001$) and 0.71 (F value = 5.31, $p < 0.025$) in the prediction of the angiographically and echocardiographically measured LV mass, respectively. According to the technique of cross validation, the stepwise logistic regression analysis was applied separately to subsets of patients. The cross-validated results confirmed those obtained in the entire study population. The multivariate analysis also derived the formulas listed in the Appendix; these formulas calculate the predictive value of LV wall thickness, volume and mass by means of electrocardiographic criteria.

DISCUSSION

The role of the electrocardiogram in the diagnosis of cardiac chamber enlargement in IDC has been assessed by several investigators, and has recently been emphasized by the Wilensky et al¹ in a study on a large number of patients compared at necropsy. Most investigations, however, have been performed in small groups of patients with IDC.²⁻⁶ On the other hand, attention has usually been paid to the electrocardiographic predictors of LV mass,^{1,2,4-6} whereas the accuracy of multiple electrocardiographic criteria in differentiating LV wall thickening from dilatation has not been previously investigated in patients with IDC.

In the present study, weak correlations, although statistically significant, were found between multiple electrocardiographic criteria for LV enlargement and LV wall thickness, volume and mass. However, as recently suggested by Devereux,⁸ the performance of electrocardiographic criteria in detecting the anatomic status in heart disease may be improved with the use of more powerful statistical methods. Accordingly, we used a multiple regression analysis, which resulted in substantially strengthened correlations compared with those obtained by using simple regression analysis.

Predictors of left ventricular wall thickness: In our series, LV wall thickness was best predicted by the combination of total 12-lead QRS amplitude, voltage

criteria of Sokolow and Lyon, overshoot and U-wave inversion.

Total 12-lead QRS amplitude as an electrocardiographic index of LV morphology was first proposed by Siegel and Roberts¹⁰ and Roberts and Waller.²⁴ They applied this criterion in different heart diseases, stating that cavity dilatation does not magnify the voltage of the QRS generated by a given mass of myocardium.²⁴⁻²⁶ More recently, the same investigators demonstrated the use of total QRS voltage in detecting LV hypertrophy in patients with IDC despite the presence of considerable cardiomegaly at necropsy.^{1,27} Furthermore, a good correlation of the Sokolow-Lyon criteria with the thickness of the ventricular septum has been observed.²⁸ However, in contrast to the general agreement that the QRS voltage is the best predictor of LV hypertrophy, Devereux et al²⁹ reported that wall thickness does not constitute an independent contributor to the generation of Sokolow-Lyon criteria. As shown in this report, inclusion of overshoot and U-wave inversion in a multivariate model for prediction of wall thickness increases the diagnostic accuracy of the method. Such an approach has not been used previously in IDC, although overshoot and U-wave inversion are frequently believed to indicate LV hypertrophy in patients without coronary artery disease.^{13,14}

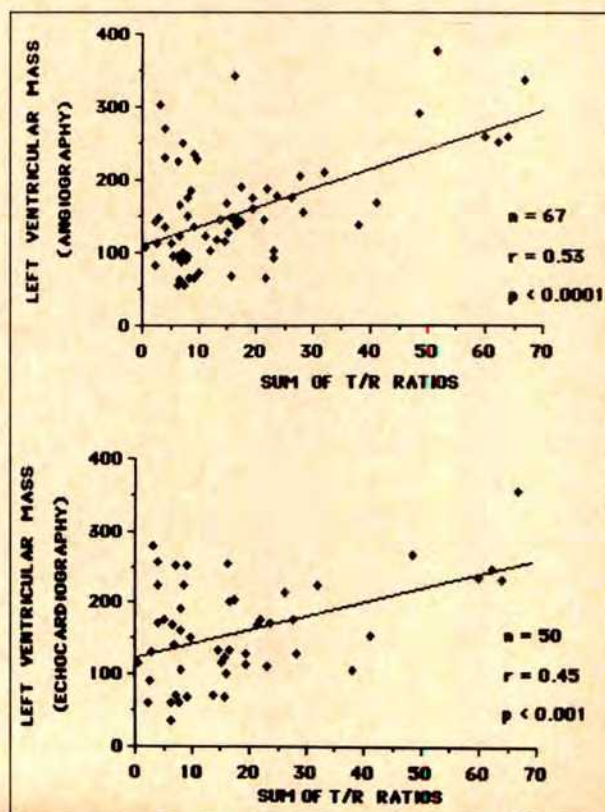


FIGURE 2. The relation between the sum of T/R-wave ratios and left ventricular mass as assessed either at angiography (upper panel) or at echocardiography (lower panel) in patients with idiopathic dilated cardiomyopathy.

Predictors of left ventricular volume: In the present study, the sum of T/R-wave ratios, the RV_6/RV_5 ratio and the Romhilt-Estes score were the factors most closely associated with LV end-diastolic volume.

As postulated by Brody,³⁰ QRS voltage should increase in the presence of an increased end-diastolic blood volume. In contrast, several studies using angiograms,³¹ echocardiography³² and nuclear imaging³³ have shown that the correlation of the QRS voltage with LV volume was either poor or less good than the relation to LV mass. Abnormalities of T wave are often thought to be less specific than the QRS voltage in the assessment of LV enlargement.⁷ However, a high correlation between variations of the T-wave amplitude and drug-induced changes in LV dimensions has been found by Feldman et al,³⁴ who have also observed that the T-wave amplitude, rather than the R-wave amplitude,³⁵ is not affected by extracardiac factors. The aforementioned discordant findings, which make the value of the QRS and T-wave voltage in the assessment of LV volume questionable, prompted us to evaluate the T/R ratio, to distinguish between primary and parallel changes in T and QRS amplitude. This ratio has the advantage of being unaffected by the distance of the recording electrode on the chest wall from the center of the ventricle.^{34,36} To our knowledge, the relation between LV morphology and T/R ratio in patients with IDC has not been previously investigated. In our series, the sum of T/R-wave ratios was the single electrocardiographic variable most closely related to LV end-diastolic volume, and its capability in predicting LV dimension was increased by the inclusion of the RV_6/RV_5 ratio in the multivariate equation. According to Spodick and Koito,^{4,37} the latter parameter appears to be directly related to LV dilatation rather than wall thickness. Indeed, the highest RV_6/RV_5 and the largest LV internal diameter were observed by these investigators in the IDC subgroup. Similar considerations apply to the point score system of Romhilt and Estes,¹² a further variable that improved the prediction of LV end-diastolic volume in our patients. This score seems to be ineffective in revealing an increased wall thickness,³⁸ whereas it is thought to correlate better with LV mass and dimension.⁷

Predictors of left ventricular mass: Total 12-lead QRS amplitude and the sum of T/R ratios were the only independent variables significantly related to an increased LV mass. These findings are in agreement with data of Wilensky¹ and Roberts²⁷ and co-workers, who pointed out the value of QRS voltage for predicting LV mass in patients with IDC. In addition, our results emphasize the use of a new electrocardiographic criterion, the sum of T/R ratios, in the assessment of LV morphology. Total 12-lead QRS amplitude and the sum of T/R ratios seem to contribute differently to pre-

diction of LV mass, because they were the strongest electrocardiographic correlates with LV wall thickness and volume, respectively. Thus, inclusion of these parameters in a multivariate equation could be profitable to better define an increased LV mass, as a consequence of either cardiac wall thickening or ventricular dilatation.

Study limitations: The first limitation of this study deals with the assessment of electrocardiographic criteria. Although great accuracy was taken in the analysis of electrocardiographic tracings, interindividual changes in chest lead placement^{34,36} and, in particular, day-to-day variability of electrocardiographic voltage³⁹ might have been possible sources of error. Another limitation lies on the computation of measurements of LV morphology from angiography and echocardiography. Previous investigators^{40,18} provided anatomic validations of the methods used in the present study. Nevertheless, we cannot rule out small errors in measuring LV wall thickness, volume and mass, although a good correlation was found between angiographically and echocardiographically assessed measurements of LV anatomy. Finally, a relative limitation is the sample size. As a consequence, we could not prospectively validate the logistic regression equations generated from our "learning" population in additional subjects. Therefore, our findings should not be generalized to other populations. Future studies are needed to verify in independent "test" series of patients with IDC the accuracy of the formulas listed in the Appendix in predicting LV wall thickness, volume and mass on the basis of electrocardiographic criteria.

In conclusion, the present study confirms that the use of a single criterion for predicting LV morphology in patients with IDC is barely effective. Multiple electrocardiographic criteria should be used to better predict LV mass and distinguish reliably between LV wall thickening and dilatation.

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APPENDIX

The model of logistic regression analysis allows calculation of the predictive value of measurements of LV morphology in patients with IDC by means of an optimized set of electrocardiographic variables. As described in the text, the final models included the following variables: total 12-lead QRS amplitude (ΣQRS , expressed in millimeters), voltage criteria of Sokolow and Lyon ($SV_1 + RV_5$, measured in millimeters), detection of U-wave inversion (transformed into 1), the presence of overshoot (transformed into 1), the sum of T/R-wave ratios ($\Sigma T/R$, dimensionless), the RV_6/RV_5 ratio (dimensionless) and the Romhilt-Estes score (in points).

Predictive values of angiographically determined LV wall thickness (LVWT, expressed in millimeters m^{-2}), end-diastolic volume (LVEDV, measured in milliliters m^{-2}) and mass (LVM, calculated in grams m^{-2}) may be calculated as follows: $LVWT = 6.12 + (1.13 \cdot \Sigma QRS) + (5.58 \cdot SV_1 + RV_5) + (3.09 \cdot U \text{ inversion}) + (0.69 \cdot \text{overshoot})$; $LVEDV = 54.35 + (4.57 \cdot \Sigma T/R) + (13.03 \cdot RV_6/RV_5) + (13.94 \cdot \text{Romhilt-Estes score})$; $LVM = 47.25 + (0.17 \cdot \Sigma QRS) + (4.68 \cdot \Sigma T/R)$.

Predictive values of echocardiographically assessed measurements of LV morphology may be calculated as follows: $LVWT = 8.35 + (6.05 \cdot \Sigma QRS) + (1.4 \cdot SV_1 + RV_5) + (1.19 \cdot U \text{ inversion}) + (3.15 \cdot \text{overshoot})$; $LVEDV = 40.29 + (5.11 \cdot \Sigma T/R) + (2.1 \cdot RV_6/RV_5) + (25.12 \cdot \text{Romhilt-Estes score})$; $LVM = 43.01 + (1.54 \cdot \Sigma QRS) + (5.55 \cdot \Sigma T/R)$.

Long-Term Assessment of Right Ventricular Diastolic Filling in Patients with Pulmonic Valve Stenosis Successfully Treated in Childhood

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Patients with severe pulmonic stenosis (PS) have right ventricular (RV) diastolic filling abnormalities detectable by tricuspid valve pulsed Doppler examination. To determine if these abnormalities persist long term after successful therapy of PS, 19 patients were examined 8 ± 3 years after PS therapy. At the time of follow-up Doppler examination, the PS gradient was 15 ± 8 mm Hg. From the tricuspid valve inflow Doppler study, the following measurements were obtained at peak inspiration: peak velocities at rapid filling (peak E) and during atrial contraction (peak A), ratio of peak E to peak A velocities, RV peak filling rate normalized for stroke volume, deceleration time, the fraction of filling in the first 0.33 of diastole as well as under the E and A waves, and the ratio of E to A area. Data from PS follow-up patients were compared with our previously reported data from 12 age-related control subjects and 14 untreated patients with PS. Patients with PS who were followed up had higher peak E velocity (0.75 ± 0.14 vs 0.59 ± 0.21 m/s), lower peak A velocity (0.47 ± 0.09 vs 0.64 ± 0.28 m/s), higher E/A velocity ratio (1.65 ± 0.33 vs 1.11 ± 0.52), higher 0.33 area fraction (0.52 ± 0.06 vs 0.34 ± 0.14), lower A area fraction (0.29 ± 0.06 vs 0.45 ± 0.21) and higher E/A area ratio (2.48 ± 0.82 vs 1.73 ± 1.05) than PS patients without treatment ($p < 0.03$). All Doppler indexes of the patients with PS who were followed up were the same as those of the control subjects except for the peak E velocity that was slightly higher (0.75 ± 0.14 vs 0.63 ± 0.11 m/s), the peak A velocity that was slightly higher (0.47 ± 0.09 vs 0.38 ± 0.09 m/s) and the E/A area ratio that was slightly lower ($2.48 \pm$

0.82 vs 3.50 ± 1.25) ($p < 0.03$). Thus, at long-term follow-up, all RV diastolic filling indexes in successfully treated patients with PS improved compared with the untreated patients and approached values found in normal subjects. These data suggest that RV diastolic filling abnormalities in patients with PS are reversible over the long term and are therefore probably related to hypertrophy rather than fibrosis and scarring. (Am J Cardiol 1991;68:648-652)

In recent years, pulsed Doppler echocardiography has been used to assess right ventricular (RV) diastolic filling in a variety of diseases including valvular pulmonic stenosis (PS), pulmonary hypertension, constrictive pericarditis and cardiac tamponade.¹⁻⁴ From the tricuspid valve Doppler recording, peak flow velocities, filling rates, and the proportion of filling in the various phases of diastole can be measured for the right ventricle.⁵ Normal values for the tricuspid valve Doppler indexes have been reported for the fetus, newborn infant and child.⁶⁻¹⁰ Recently, we reported the use of these Doppler indexes to detect abnormal patterns of RV diastolic filling in children with PS.⁴ Children with PS had a decreased percentage of the total Doppler area in the first third of diastole and an increased percentage of the total Doppler area under the A wave suggesting a relative shift of RV filling to late diastole. Furthermore, these diastolic filling abnormalities did not improve immediately after successful relief of the RV outflow obstruction, suggesting that afterload mismatch was not the direct cause of the observed diastolic filling abnormalities.

In this study, we hypothesized that RV hypertrophy is the cause of the impaired RV early diastolic relaxation found in children with valvular PS. Furthermore, if the RV diastolic filling abnormalities were caused by hypertrophy alone rather than fibrosis or scarring, then these abnormalities should return to normal as hypertrophy regresses over the long-term follow-up period after successful relief of PS. To test this hypothesis, we

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assessed RV diastolic filling using pulsed Doppler echocardiography in 19 patients who were examined 8 ± 3 years after successful relief of PS.

METHODS

Patients: The study included 19 patients who were examined 8 ± 3 years (mean \pm standard deviation) after successful relief of PS (Table I). These patients were randomly selected from all patients with PS undergoing routine follow-up evaluation in the outpatient clinic. Selection criteria included: (1) evidence by Doppler examination of successful relief of PS (peak gradient <25 mm Hg), (2) absence of additional congenital defects such as tricuspid stenosis or left-to-right shunts that might alter the tricuspid valve Doppler recording, and (3) absence of significant tricuspid regurgitation that might mask RV diastolic filling abnormalities.

The PS follow-up group was 5 to 19 years old (mean 10.9) and weighed 18 to 83 kg (mean 45.2). Ten patients had previous pulmonary balloon valvuloplasty and 9 had surgical pulmonary valvotomy. Ten patients were treated before and 9 were treated after the age of 2 years. Data from PS patients at long-term follow-up were compared with our previously reported data from 12 age-related control subjects and 14 untreated patients with severe PS (Table I).⁴

Echocardiographic examinations: All study participants underwent a complete 2-dimensional and Doppler echocardiographic examination with the use of a 128-element phased-array ultrasound system and a variety of transducers appropriate for patient size. Tricuspid valve Doppler examinations were obtained from the parasternal short-axis or apical 4-chamber view. The sample volume was positioned so as to record the maximal velocities through the valve (usually near the tips of the leaflets). Based on prior studies with use of simultaneous thermister and tricuspid valve Doppler recordings, the velocities through the tricuspid valve vary significantly throughout the respiratory cycle with maximal velocities occurring at peak inspiration.⁸ Therefore, to obtain all Doppler measurements at a standard time in the respiratory cycle, only beats recorded at peak inspiration were used.

From the Doppler spectral recordings, the peak velocities during rapid ventricular filling (peak E) and during atrial contraction (peak A) were measured, and the ratio of peak E to peak A velocities was calculated. To determine the Doppler pattern of RV filling, several areas under the Doppler tracing were measured using previously described methods: (1) the total area under the velocity envelope throughout diastole; (2) the area under the velocity curve for the first 33% of diastole (0.33 area); (3) the E area, or the triangular area

TABLE I Demographic Data for the Three Patient Groups

	Control Subjects	PS F/U	PS Pre
No. of patients	12	19	14
Age (years)	8.6 (4.5–16)	10.9 (5–19)*	5.1 (0.4–18)†
Weight (kg)	32.7 \pm 15.4	45.2 \pm 21.7*	21.6 \pm 20†
Height (cm)	133 \pm 20	145 \pm 25*	103 \pm 32†

*p < 0.01 compared with PS pre; †p < 0.01 compared with control subjects.
F/U = follow-up; Pre = untreated; PS = pulmonary stenosis.

formed by extrapolating a straight line down from the peak E velocity to the baseline; and (4) the A area, or the triangular area formed in a similar manner under the peak A velocity.¹¹ To determine the percentage of the total velocity envelope occupied by the individual areas, the area or filling fractions were calculated as the individual areas divided by the total area under the Doppler tracing. Also, the ratio of E and A areas was calculated. The peak filling rate normalized for stroke volume was calculated as the peak E velocity divided by the total velocity time integral,¹² and the deceleration time was measured from the peak E velocity to the time when the Doppler curve returned from the peak E velocity to the baseline.¹³

Color, pulsed and continuous-wave Doppler examinations of the pulmonary valve were obtained from parasternal or subcostal views. With use of the view that provided the highest value for the peak velocity of the PS jet, the peak instantaneous pressure gradient across the pulmonary valve was calculated from the Bernoulli equation.⁶ Pulmonary insufficiency was diagnosed using color flow imaging techniques and was considered to be significant if the M-mode echocardiographic examination showed evidence of paradoxical septal motion or RV end-diastolic dimension $>95\%$ for body surface area, or both.¹⁴

All Doppler examinations were recorded at a paper speed of 100 mm/s. The Doppler areas were traced from the paper recording using a digitizing tablet with a crosswire cursor, a personal computer and commercially available computer software. The Doppler velocities and areas were measured by tracing the outermost border of the spectral recordings.

Statistical analysis: Three cardiac cycles were measured and averaged to obtain each Doppler value. Statistical comparisons between the PS follow-up patients and the control subjects and between the untreated PS patients and the PS follow-up patients were obtained using unpaired *t* tests and Bonferroni's correction for multiple comparisons. To determine if differences in RV diastolic filling patterns existed between different patients in the PS follow-up group, the group was divided into several subgroups which were then compared using unpaired *t* tests. Subgroup analyses included: (1) comparison of PS follow-up patients >2 years old at

TABLE II Tricuspid Valve Doppler Measurements

Measurement	Control Subjects	PS F/U	PS Pre
Peak E (m/s)	0.63 ± 0.11	0.75 ± 0.14*†	0.59 ± 0.21
Peak A (m/s)	0.38 ± 0.09	0.47 ± 0.09*†	0.64 ± 0.28*
E/A vel.	1.74 ± 0.51	1.65 ± 0.33†	1.11 ± 0.52*
Total VTI (m)	0.12 ± 0.02	0.13 ± 0.03	0.12 ± 0.03
0.33 area fx	0.51 ± 0.12	0.52 ± 0.08†	0.34 ± 0.14*
E area fx	0.71 ± 0.08	0.67 ± 0.07	0.57 ± 0.19*
A area fx	0.24 ± 0.10	0.29 ± 0.06†	0.45 ± 0.21*
E/A area	3.50 ± 1.25	2.48 ± 0.82*†	1.73 ± 1.05*
Decel. time (s)	0.14 ± 0.02	0.12 ± 0.02†	0.09 ± 0.04*
PFR/SV (SV/s)	5.23 ± 0.56	5.79 ± 1.08	5.28 ± 1.96
Heart rate (beats/min)	77 ± 13	75 ± 13†	99 ± 27*

*p < 0.03 compared with control subjects; †p < 0.03 compared with PS pre. Values are mean ± standard deviation.

A = peak velocity at atrial contraction; E = peak velocity in early diastole; Decel. = deceleration; fx = fraction; F/U = follow-up; PFR/SV = peak filling rate normalized to stroke volume; Pre = untreated; PS = pulmonary stenosis; vel. = velocity; VTI = velocity time integral.

the time of therapy and those <2 years at the time of therapy; (2) comparison of PS follow-up patients treated with surgery to those treated with balloon valvuloplasty; and (3) analysis of a subgroup of PS follow-up patients formed by exclusion of all patients with significant pulmonary insufficiency and RV diastolic dimension >95% for body surface area. A two-tailed p value <0.03 was used to indicate a significant intergroup difference. All values are mean ± standard deviation.

RESULTS

Patients: The PS follow-up patients did not differ from the control subjects in age, height, weight or heart rate. Compared with untreated PS patients, the PS follow-up patients were older, had greater heights and weights, and had slower heart rates. Before treatment, the PS follow-up patients had the same pulmonary valve gradient as the untreated PS patients (67 ± 18 vs 71 ± 35 mm Hg, $p = 0.66$). After treatment, the PS follow-up patients had a significantly lower pulmonary valve gradient (15 ± 8 mm Hg).

Echocardiographic studies: COMPARISONS OF PULMONIC STENOSIS FOLLOW-UP PATIENTS WITH CONTROL SUBJECTS AND UNTREATED PULMONIC STENOSIS PATIENTS: Mean values for the Doppler measurements of the 3 patient groups are listed in Table II. The peak E velocity of the PS follow-up patients was significantly higher than that of the untreated PS patients and the control subjects. The peak A velocity of the PS follow-up patients was significantly lower than that of the untreated PS patients but still higher than that of control subjects. As a result, the E/A velocity ratio of PS follow-up patients was increased to a value not different from that found in normal subjects.

Compared with untreated PS patients, the 0.33 area fraction of the PS follow-up patients had increased significantly to a value not different from that found in

control subjects. Likewise, the E area fraction of the PS follow-up patients was higher than that of the untreated PS patients ($p = 0.05$) and the same as that of the control subjects. The A area fraction of the PS follow-up patients had decreased significantly compared with that of untreated PS patients and was the same as that of normal subjects. As a result, the E/A area ratio of the PS follow-up group was significantly higher than that of untreated PS patients but did not quite reach the value found in normal subjects.

The deceleration time of the PS follow-up patients was longer than that found in the untreated PS patients but the same as that found in normal subjects. The normalized peak filling rates of the 3 patient groups were not significantly different.

SUBGROUP ANALYSIS: To determine the effect of age at the time of treatment on the observed Doppler findings, the PS follow-up group was divided into 2 subgroups: (1) patients >2 years old at the time of therapy ($n = 10$), and (2) patients <2 years old at the time of therapy ($n = 9$). No differences were found in any diastolic filling indexes between the 2 subgroups.

To determine the effect of the type of therapy on the observed Doppler findings, the PS follow-up group was divided into 2 subgroups: (1) patients treated with surgery ($n = 9$), and (2) patients treated with balloon valvuloplasty ($n = 10$). No differences were found in any of the RV diastolic filling indexes between the 2 subgroups.

To determine if significant pulmonary insufficiency had an effect on the observed Doppler findings, a subgroup of PS follow-up patients was formed by excluding all patients ($n = 4$) with pulmonary insufficiency and RV diastolic dimension >95% for body surface area. Elimination of these 4 patients did not change any of the statistical comparisons between the PS follow-up patients and the untreated PS and control groups.

DISCUSSION

In a previous study, we showed that children with severe PS have RV diastolic filling abnormalities detectable with Doppler echocardiography.⁴ In these children, the tricuspid Doppler examination showed a decreased percentage of the total Doppler area in the first third of diastole and an increased percentage of the total Doppler area under the A wave, suggesting a relative shift of RV filling to late diastole. This abnormal tricuspid Doppler pattern resembles the mitral Doppler pattern I observed by Appleton et al¹³ in patients with impaired left ventricular early diastolic relaxation and normal left ventricular filling pressures. Immediately after balloon valvuloplasty and successful relief of the high afterload, RV diastolic filling abnormalities per-

sisted, suggesting that afterload mismatch was not the cause of the filling abnormalities. In this long-term follow-up study, all RV diastolic filling indexes in successfully treated PS patients improved compared with untreated PS patients, and approached values found in normal subjects. These data suggest that RV diastolic filling abnormalities in PS patients are reversible and are, therefore, probably related to hypertrophy rather than fibrosis and scarring. RV mass was not assessed owing to the lack of an accurate means of measuring it noninvasively; however, all untreated PS patients had echocardiographic evidence of severe RV hypertrophy while the PS follow-up patients had little or no evidence of RV hypertrophy.

Possible mechanisms of diastolic filling abnormalities: Courtois et al¹⁵ recently showed that a pattern of diastolic apex to inflow pressure gradients exists in the right ventricle during early and late diastole, similar to that reported in the left ventricle.¹⁶ In the right ventricle, however, the lowest early diastolic pressures are usually recorded in the outflow tract rather than in the apex. The form and timing of the regional ventricular pressure gradients found in their study suggest that mechanical suction of blood into the ventricular cavity is the primary mechanism of RV filling in early diastole. Mechanisms that probably contribute to mechanical suction include downward motion of the right ventricle during systole, active contraction of muscle fibers below equilibrium and resultant storage of elastic energy, and end-systolic deformation of the walls of the RV outflow tract. In the latter mechanism, blood continues to leave the ventricle after contraction has ended, thus causing the shape of the RV outflow tract to be distorted, elastic energy to be stored in the myocardium, and the walls of the outflow tract to recoil in early diastole. The importance of this mechanism is supported by the finding of the lowest early diastolic pressure in the RV outflow tract and the observation that significant narrowing of the outflow tract occurs at end-systole.¹⁵

In untreated PS patients, severe RV hypertrophy can lead to reduced end-systolic deformation of the RV outflow tract, less elastic recoil in early diastole, and a higher minimum RV pressure in early diastole. With a higher minimum RV diastolic pressure, the early diastolic pressure gradient and, thus, the peak E velocity are decreased as was observed in our untreated PS patients. At long-term follow-up, the return of the peak E velocity and the percent filling in early diastole toward normal values suggests that the end-systolic deformation of the outflow tract walls is restored as RV hypertrophy regresses.

In normal subjects, the tricuspid deceleration time is longer than the mitral deceleration time, suggesting

that the thin-walled right ventricle is a less effective decelerator than the thicker-walled left ventricle.¹⁵ In untreated PS patients, we found a shortened tricuspid deceleration time compared with age-related normal subjects. It is likely that the thick-walled right ventricle of untreated PS patients quickly generates a reversed pressure gradient of sufficient magnitude to decelerate flow in early diastole. As hypertrophy regresses after successful relief of PS, the thin-walled right ventricle requires a longer period of time to generate a reverse pressure gradient, and thus the increase in deceleration time to normal values in our follow-up patients.

Factors affecting the tricuspid valve Doppler indexes: Diastolic indexes of RV relaxation can be influenced by several factors including age, heart rate, respiration and RV loading conditions. Throughout childhood, the tricuspid Doppler indexes are independent of age beyond the neonatal period⁵⁻⁸ and, thus, it is unlikely that age contributed to the observed improvement in RV diastolic filling. In several recent studies, tricuspid Doppler indexes have been unrelated or only weakly related to heart rate.^{17,18} In this study, the improved RV filling cannot be explained on the basis of heart rate since the heart rates of the control and PS follow-up patients were not different. From expiration to inspiration in normal children, the tricuspid peak E velocity increases by 26%, the peak A velocity increases by 18%, and the E/A velocity ratio remains unchanged.⁸ In this study, the effects of respiration were eliminated by measuring only beats at maximal inspiration. The presence of tricuspid or pulmonary insufficiency may alter the early diastolic transvalvular pressure gradient and, thus, affect the tricuspid Doppler indexes. In this study, no patient had significant tricuspid insufficiency, and exclusion of 4 patients with pulmonary insufficiency did not alter the results.

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Factors Influencing Doppler Indexes of Left Ventricular Filling in Healthy Persons

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Ninety-three healthy persons aged 11 to 91 years were studied to assess the factors influencing Doppler indexes of left ventricular (LV) diastolic filling. The effects of physical activity, alcohol consumption and smoking were tested in addition to those of age, sex, heart rate, body mass index, blood pressure, left atrial diameter, and LV end-diastolic diameter, wall thickness, mass and fractional shortening. The data were fitted stepwise into multiple linear regression models both in the total population and in 3 groups aged <40, 40 to 60 and >60 years. In the total population, age explained 45 to 68% of the variation in the peak early and late diastolic velocities, their ratio, deceleration of the early velocity, atrial filling fraction and peak filling rate normalized to mitral stroke volume. With advancing age — and with increases in either body mass index, heart rate, diastolic blood pressure or LV mass — the indexes of early filling decreased, whereas with regular modest use of alcohol or regular aerobic exercise they increased ($p < 0.05$ for all). In the middle-aged subjects, gender explained 32 to 57% of the variation in the peak atrial velocity, early to atrial peak velocity ratio and atrial filling fraction; the peak velocity ratio measured 1.4 ± 0.3 (mean \pm standard deviation) in men vs 1.0 ± 0.2 in women ($p < 0.001$).

In conclusion, many constitutional and physiologic factors and even life-style can influence the Doppler indexes of LV filling. This demonstrates the exquisite sensitivity of the method but indicates also that individual measurements must be interpreted with caution.

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The study of left ventricular (LV) filling by Doppler ultrasound is based on recording the transmitral flow velocity throughout the diastolic period.¹ Velocity-derived indexes are sensitive to filling impairment in many types of heart disease,^{2–5} and, given certain preconditions, they may even distinguish poor relaxation from abnormal compliance.^{6–8} The interpretation of individual Doppler measurements can be difficult, however, because they are influenced not only by changes in the intrinsic LV diastolic properties, but also by age, heart rate, valvular disease, loading conditions, and contractility of both ventricular and atrial myocardium.^{6–8}

As with any new diagnostic technique, the behavior and determinants of the Doppler filling indexes in health should first be thoroughly known. Although many valuable studies have been reported,^{9–18} they have, with few exceptions,^{12,14–16} focused on only 1 factor at a time. Our purpose was to examine the influence on the Doppler measurements of as many cardiac and noncardiac factors as was reasonable to assess in a non-invasive laboratory. The factors tested included data on habitual physical activity, smoking and alcohol consumption in addition to age, sex, body size, and a number of cardiovascular measurements. To find out the independent explanatory power of each determinant, the data were fitted into multivariate models in addition to performing univariate analyses when appropriate.

METHODS

Study group: We studied 93 persons (54 men, 39 women) aged 11 to 91 years (mean 45). They were mostly nonpaid volunteers from the out-of-hospital population, but a few elderly persons were examined while in the hospital for minor noncardiac reasons. All were caucasians and free of heart disease according to the following criteria: (1) no history of cardiovascular or any other chronic disease, (2) no chest pain or dyspnea on effort, (3) no use of whatever regular medication, (4) normal findings on physical examination, (5) normal 12-lead electrocardiogram, and (6) normal findings on a combined 2-dimensional and M-mode echocardiographic examination. The population was divided into 3 age groups: (1) <40 years ($n = 40$; 23 men, 17 women); (2) 40 to 60 years ($n = 32$; 19 men, 13 women); and (3) >60 years ($n = 21$; 12 men, 9 women).

TABLE I Coefficients of Repeatability* of Doppler Indexes of Left Ventricular Filling in Healthy Persons

Doppler Index	Repeatability of Measurement (n = 10)	Repeatability of Examination (n = 8)
Peak early diastolic velocity (cm/s)	1.1	7.2
Peak atrial velocity (cm/s)	0.9	5.4
Early to atrial peak velocity ratio	0.03	0.44
Relaxation time (ms)	5	21
Acceleration of early flow (cm/s ²)	53	434
Deceleration of early flow (cm/s ²)	32	120
Atrial filling fraction	0.02	0.06
Peak filling rate (s ⁻¹)	0.38	0.68

*The coefficients represent the 95% confidence intervals for absolute differences in paired determinations.²³

Evaluation of individual subjects: We questioned the subjects on their habitual physical activity, alcohol consumption and smoking, and classified them either as physically active or nonactive, regular or nonregular drinkers, and smokers or nonsmokers. They were considered physically active (n = 39) if they did >30 minutes of aerobic exercise (jogging, swimming, cycling, cross-country skiing) ≥ 3 times a week; otherwise they were considered nonactive (n = 54). Subjects drinking alcohol ≥ 2 times a week (n = 41) were considered regular drinkers; all the others (including the teetotalers) were non-regular drinkers (n = 52). Fourteen subjects smoked daily, 79 were nonsmokers.

The resting cuff blood pressure, body height and body weight were measured at the time of the study. Body mass index was calculated as weight (kg) divided by the square of height (m).

We performed ultrasound studies with an instrument combining a spectral analyzer-based pulsed Doppler velocimeter and a strip-chart recorder with a mechanical sector scanner (Hewlett-Packard 77020A). The transducer's frequency was 2.5 MHz. The subjects were in a postabsorptive state and rested supine for 20 to 30 minutes preceding the examination. The study consisted of 2-dimensional imaging followed by M-mode recordings of left ventricular and left atrial dimensions and Doppler velocimetry of mitral flow. An external phonocardiogram and an electrocardiogram were recorded simultaneously with the M-mode and Doppler tracings. The chart speed was 50 mm/s. Our protocol was approved by the institutional ethical committee, and each participant gave a verbal informed consent.

M-mode echocardiography: For the LV study, we positioned the M-mode cursor line across the left ventricle just below the mitral valve tips. The end-diastolic LV diameter and the septal and posterior wall thickness were measured at the onset of Q-wave on electrocardiogram. The mean wall thickness was calculated as (sep-

tal thickness + posterior wall thickness)/2. The end-systolic LV diameter was measured as the shortest systolic dimension. Fractional shortening was calculated as (end-diastolic diameter - end-systolic diameter)/end-diastolic diameter. The LV mass was determined by the method of Devereux et al.¹⁹ The left atrial diameter was measured as the longest systolic dimension on recordings taken through the aortic root and left atrium.²⁰

Doppler echocardiography: We used the apical 4- or 2-chamber view to direct the Doppler cursor line through the mitral orifice as parallel as possible to the assumed diastolic inflow. The site of the sample volume was 0 to 1 cm below the mitral annulus, and it was adjusted according to the audible and visible signals to get a sharply defined velocity waveform. No angle correction was made. The recording consisted of a minimum of 5 cycles taken during quiet expiration.

The following Doppler indexes were measured on an x-y digitizing tablet as recently detailed²¹: (1) peak early diastolic velocity; (2) peak late diastolic (atrial) velocity; (3) early to atrial peak velocity ratio; (4) the time from the aortic component of the second heart sound to the point of peak early velocity, i.e., the relaxation time; (5) the acceleration of the early flow; (6) the deceleration of the early flow; (7) the ratio of the atrial to the total velocity-time integral, i.e., the atrial filling fraction; and (8) the ratio of the peak early velocity to the total velocity-time integral, i.e., the peak filling rate normalized to mitral stroke volume.²² Five cycles were analyzed and averaged for each measurement.

We studied the repeatability of our Doppler method by blindly tracing twice the velocity curves of 10 subjects (repeatability of measurement), and by examining 8 subjects twice at an interval of 1 to 6 months (repeatability of examination). The coefficients of repeatability (Table I) were calculated as suggested by Bland and Altman.²³

Statistical methods: The primary objective was to assess the relation of the Doppler indexes (dependent variables) to the explanatory factors (independent variables) included in our study. We performed such analyses both in the total population and in the 3 age-based subgroups using stepwise multiple linear regression analysis (SPSS statistical software). The explanatory factors were the clinical and echocardiographic characteristics listed in Table II, as well as age, sex and dichotomized data on habitual physical activity (active = 1, nonactive = 0), alcohol use (regular drinker = 1, non-regular drinker = 0) and smoking (smoker = 1, non-smoker = 0). The criterion for including a factor in the model was $p < 0.05$. The square of the multiple cor-

relation coefficient (R^2) was calculated for the total equation and the R^2 change separately for each factor accepted into the model. These figures are given in percentages and they indicate how much of the variation in any Doppler index was explained by the total equation

and by each individual factor. When appropriate, univariate associations and group differences were studied using Pearson's correlation coefficients and Student's 2-tailed t test. The numerical data are given as mean \pm standard deviation.

TABLE II Clinical and M-Mode Echocardiographic Characteristics of the Study Group

Characteristic	Age Subgroup			
	All Subjects (n = 93)	< 40 Years (mean age 27) n = 40	40 to 60 Years (mean age 50) n = 32	> 60 Years (mean age 73) n = 21
Body mass index (kg/m ²)	28 \pm 9	26 \pm 10	30 \pm 8	28 \pm 9
Heart rate (beats/min)	66 \pm 11	66 \pm 9	65 \pm 12	69 \pm 12
Systolic blood pressure (mm Hg)	127 \pm 18	119 \pm 13	130 \pm 18	137 \pm 18
Diastolic blood pressure (mm Hg)	76 \pm 11	71 \pm 9	81 \pm 9	79 \pm 12
Left ventricular end-diastolic diameter (mm)	49 \pm 5	49 \pm 5	49 \pm 4	50 \pm 5
Fractional shortening	0.35 \pm 0.06	0.36 \pm 0.05	0.36 \pm 0.04	0.32 \pm 0.08
Mean wall thickness (mm)	9.0 \pm 1.0	8.6 \pm 1.0	9.3 \pm 1.0	9.2 \pm 1.1
Left ventricular mass (g)	179 \pm 44	165 \pm 47	190 \pm 43	191 \pm 55
Left atrial diameter (mm)	32 \pm 4	30 \pm 4	33 \pm 3	34 \pm 5

The data are mean \pm standard deviation.

TABLE III Doppler Indexes on Left Ventricular Filling in the Study Group

Doppler Index	Age Subgroup			
	All Subjects (n = 93)	< 40 Years (mean age 27) n = 40	40 to 60 Years (mean age 50) n = 32	> 60 Years (mean age 73) n = 21
Peak early diastolic velocity (cm/s)	63 \pm 14	73 \pm 9	58 \pm 11	52 \pm 11
Peak atrial velocity (cm/s)	48 \pm 15	38 \pm 8	48 \pm 10	66 \pm 16
Early to atrial peak velocity ratio	1.5 \pm 0.6	2.0 \pm 0.5	1.2 \pm 0.3	0.8 \pm 0.02
Relaxation time (ms)	149 \pm 25	139 \pm 19	152 \pm 26	164 \pm 26
Acceleration of early flow (cm/s ²)	858 \pm 250	925 \pm 227	806 \pm 130	812 \pm 302
Deceleration of early flow (cm/s ²)	-423 \pm 120	-525 \pm 119	-372 \pm 103	-308 \pm 90
Atrial filling fraction	0.32 \pm 0.12	0.23 \pm 0.06	0.34 \pm 0.07	0.45 \pm 0.09
Peak filling rate (s ⁻¹)	4.9 \pm 0.9	5.5 \pm 0.6	4.6 \pm 0.7	4.0 \pm 0.7

The data are mean \pm standard deviation.

TABLE IV Regression Models for Doppler Filling Indexes in the Total Study Group

Index	Model	$R^2(\%)*$	Values	
			F†	p†
Peak early diastolic velocity (cm/s)	-0.41 \times age (45%) - 0.95 \times BMI (6%) + 104	51	46.1	0.0001
Peak atrial velocity (cm/s)	0.53 \times age (56%) + 0.39 \times HR (7%) - 6.4 \times ALC (4%) + 0.19 \times DBP (2%) - 14	69	48.6	0.0001
Early to atrial peak velocity ratio	-0.02 \times age (68%) - 0.03 \times BMI (4%) - 0.01 \times HR (3%) - 0.008 \times DBP (1%) + 4.6	76	69.1	0.0001
Relaxation time (ms)	0.5 \times age (18%) - 12.5 \times ALC (6%) - 0.57 \times HR (7%) + 1.5 \times BMI (4%) + 135	35	11.6	0.0001
Acceleration of early flow (cm/s ²)	-14.9 \times BMI (4%) + 1208	4	4.2	0.04
Deceleration of early flow (cm/s ²)	4.4 \times age (46%) + 7.0 \times BMI (3%) - 786	49	42.1	0.0001
Atrial filling fraction	0.004 \times age (61%) + 3.7 \times HR (12%) + 5.4 \times BMI (4%) - 0.04 \times ALC (3%) + 0.002 \times DBP (2%) - 0.03 \times ACT (1%) - 0.3	83	71.5	0.0001
Peak filling rate (s ⁻¹)	-0.03 \times age (48%) + 0.02 \times HR (9%) + 0.34 \times ALC (5%) - 0.04 \times BMI (3%) + 0.31 \times ACT (2%) - 0.03 \times LVM (2%) + 5.6	69	30.8	0.0001

* R^2 (the square of the multiple correlation coefficient) indicates how much of the variation in the Doppler index is explained by the overall model. The percentage in parentheses after each factor indicates the change in R^2 resulting from the addition of the factor into the model.
†F and p values for the statistical significance of the model; the inclusion criterion for each individual factor was $p < 0.05$.
ACT = physical activity (active = 1, nonactive = 0); ALC = alcohol use (regular = 1, nonregular = 0); BMI = body mass index; DBP = diastolic blood pressure; HR = heart rate; LVM = left ventricular mass.

RESULTS

The clinical and M-mode echocardiographic data are summarized in Table II and the Doppler data in Table III, both for the whole study population and for the 3 groups of age.

Determinants of the Doppler indexes in the total study population (Table IV): Age alone explained 45 to 68% of the variation in the peak early and late diastolic velocities, the ratio, atrial filling fraction and peak filling rate (Figure 1). Although heart rate, body mass index, alcohol consumption, physical activity, diastolic blood pressure and LV mass also had statistically significant effects on ≥ 1 Doppler variable ($p < 0.05$), their contribution was clearly smaller.

Systolic blood pressure, left atrial diameter, LV end-diastolic diameter and mean wall thickness each showed statistically significant univariate associations with ≥ 1 Doppler index, but none had independent influence in multivariate analysis. Systolic blood pressure, for instance, correlated directly with the peak atrial velocity ($r = 0.49$) and atrial filling fraction ($r = 0.50$) and inversely with the peak velocity ratio ($r = -0.48$) and the peak filling rate ($r = -0.38$) ($p < 0.001$ for all). However, it was also age-related ($r = 0.48$, $p < 0.001$) and had no effect after age had been taken into account. Likewise, left atrial diameter correlated with peak atrial velocity ($r = 0.35$) and atrial filling fraction ($r = 0.28$) ($p < 0.01$), but neither as-

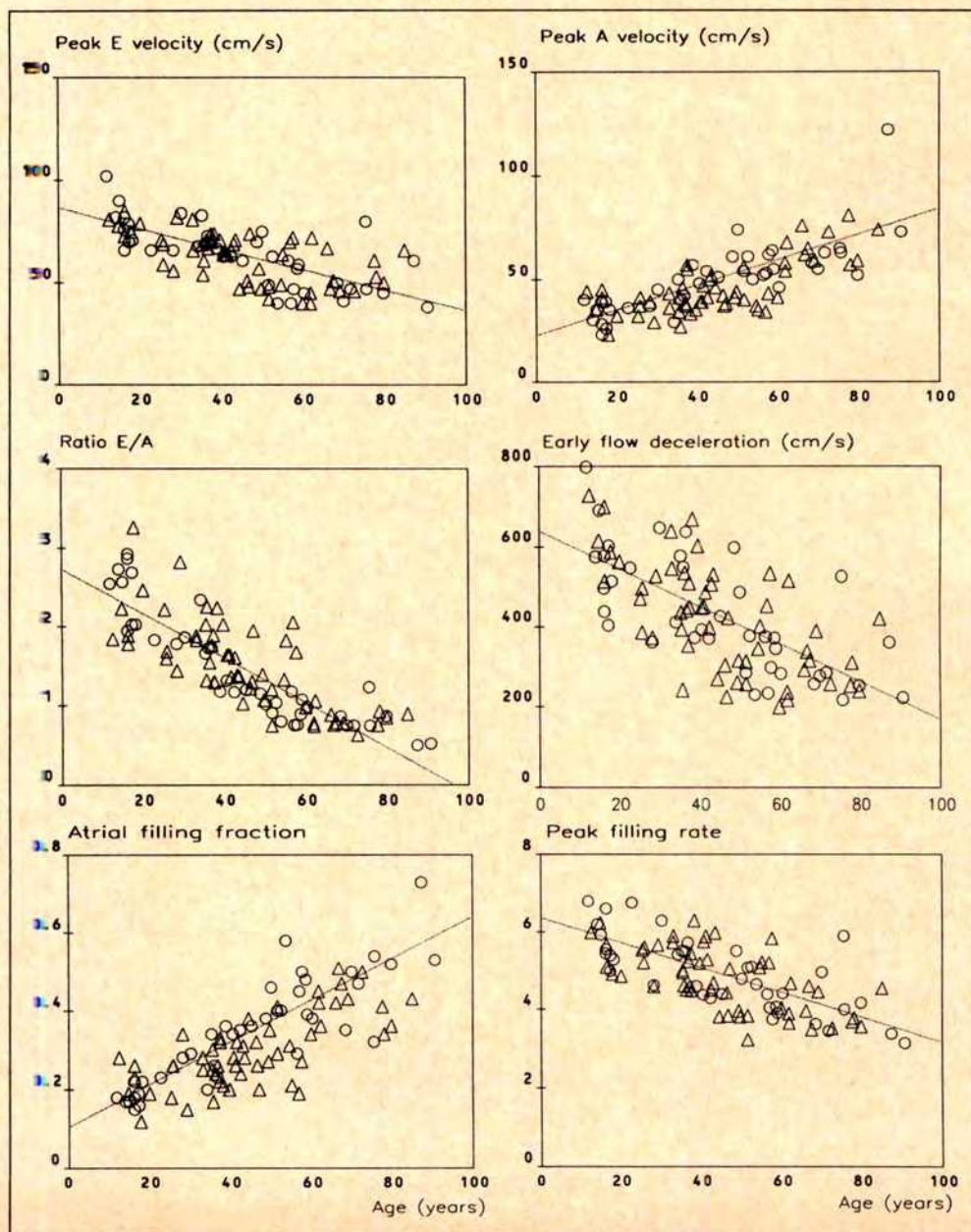


FIGURE 1. Peak early diastolic (E) velocity, peak late diastolic (A) velocity, early to atrial velocity (E/A) ratio, deceleration of the early flow velocity, atrial filling fraction and peak filling rate normalized to mitral stroke volume as a function of age in 93 healthy persons aged 11 to 91 years. The triangles and circles indicate men and women, respectively.

TABLE V Regression Models for Doppler Filling Indexes in Different Age Subgroups

Index	Model	R ² (%)*	Values	
			F†	pt
Age > 40 Years				
Peak early diastolic velocity (cm/s)	-0.46 × age (22%) + 86	22	10.8	0.02
Peak atrial velocity (cm/s)	0.51 × HR (22%) + 0.43 × age (23%) - 8	45	14.9	0.0001
Early to atrial peak velocity ratio	-0.03 × age (30%) - 0.03 × HR (22%) + 4.7	52	20.6	0.0001
Relaxation time (ms)	2.6 × BMI (17%) - 1.0 × HR (18%) - 9.8 × ALC (7%) + 150	42	8.7	0.0002
Deceleration of early flow (cm/s ²)	5.0 × age (16%) - 660	16	7.0	0.01
Atrial filling fraction	0.006 × age (25%) + 0.003 × HR (30%) - 0.06 × ALC (11%) - 0.0003 × LVM (4%) - 0.08	70	19.8	0.0001
Peak filling rate (s ⁻¹)	0.03 × HR (19%) - 0.06 × BMI (11%) + 4.8	30	8.2	0.001
Age 40 to 60 Years				
Peak early diastolic velocity (cm/s)	133 × FS (29%) + 9.5	29	12.5	0.001
Peak atrial velocity (cm/s)	-14.6 × sex‡ (57%) + 56.8	57	40.2	0.0001
Early to atrial peak velocity ratio	0.39 × sex (32%) + 1.0	32	14.1	0.0007
Relaxation time (ms)	3.3 × LVEDD (27%) - 20 × ALC (14%) - 1.3	41	10.3	0.0004
Deceleration of early flow (cm/s ²)	-1050 × FS (20%) + 9	20	7.6	0.01
Atrial filling fraction	-0.12 × sex (47%) + 0.4	47	27.0	0.0001
Age > 60 Years				
Peak early diastolic velocity (cm/s)	10.3 × ACT (20%) + 49	20	4.6	0.045
Peak atrial velocity (cm/s)	1.0 × age (27%) + 0.1 × LVM (18%) - 32	45	7.4	0.005
Early to atrial peak velocity ratio	0.17 × ACT (40%) - 0.006 × DBP (14%) + 1.2	54	10.4	0.001
Relaxation time (ms)	1.8 × age (36%) + 30	36	10.7	0.004
Atrial filling fraction	0.004 × HR (23%) + 0.004 × DBP (24%) - 0.12	47	7.9	0.004
Peak filling rate (s ⁻¹)	0.03 × HR (26%) - 0.03 × DBP (22%) + 0.62 × SMO (17%) + 4.4	65	10.2	0.001

*R² (the square of the multiple correlation coefficient) indicates how much of the variation in the Doppler index is explained by the overall model. The percentage in parentheses after each factor indicates the change in R² resulting from the addition of the factor into the model.
†F and p values for the statistical significance of the model; the inclusion criterion for each individual factor was p < 0.05.
‡Men = 1; women = 0.
FS = fractional shortening; LVEDD = left ventricular end-diastolic diameter; SMO = smoking (smoker = 1, nonsmoker = 0); other abbreviations as in Table IV.

sociation was statistically significant in multivariate analysis.

Determinants of the Doppler indexes in young persons (Table V): Age and heart rate were the most important factors in the young and accounted together for 45 to 55% of the variation in the peak atrial velocity, peak velocity ratio and atrial filling fraction. Body mass index had a modest effect on the relaxation time and peak filling rate, and alcohol had a comparable but directionally opposite effect on the relaxation time and atrial filling fraction.

Determinants of the Doppler indexes in middle age (Table V): Gender was the strongest explanatory factor and accounted for 32 to 57% of the variation in the peak atrial velocity, peak velocity ratio and atrial filling fraction. The peak atrial velocity measured 42 ± 6 cm/s in men ($n = 19$) vs 57 ± 7 cm/s in women ($n = 13$) ($p < 0.001$), the peak velocity ratio 1.4 ± 0.3 in men vs 1.0 ± 0.2 in women ($p < 0.001$), and the atrial filling fraction 0.29 ± 0.10 in men vs 0.41 ± 0.10 in women ($p < 0.001$). Alcohol had an effect on the relaxation time also in middle-aged persons.

Determinants of the Doppler indexes in old age (Table V): In subjects aged >60 years, age, heart rate, diastolic blood pressure and physical activity each had a modest independent effect on at least 1 Doppler variable. The single most conspicuous effect was that of

physical activity on the peak velocity ratio, which measured 0.95 ± 0.15 in the active elderly ($n = 7$) vs 0.74 ± 0.12 in their nonactive age mates ($n = 14$) ($p = 0.01$).

DISCUSSION

Our results demonstrate that the Doppler indexes of LV filling are influenced by many constitutional and physiologic determinants and even by such characteristics of life style as alcohol consumption and physical exercise. However, in healthy subjects they are insensitive to such important variables as systolic blood pressure, left atrial size, and LV size, wall thickness and systolic function.

Age: As in many earlier studies,^{10-15,24,25} age was the most powerful determinant of the Doppler filling indexes in our study population. Acceleration of the early flow velocity was the only measurement unrelated to age, but the validity of this finding is questionable due to the poor repeatability of this index (see Table I). The pattern of changes with age in the Doppler measurements suggests a reduction in the rate of LV relaxation.^{6,7} To all appearance, it represents an alteration ("aging") of the intrinsic diastolic properties of the heart muscle.

Sex: Although sex did not influence the Doppler filling indexes throughout the age range of our study pop-

ulation, it had a significant effect in subjects aged 40 to 60 years. Five earlier studies,^{12,14-16,24} 3 of them focusing on adult patients,^{12,14,24} compared Doppler indexes between men and women without finding a comparable difference. Our own data are so consistent, however, that the odds are >1,000 to 1 against a chance finding. The most likely explanation of these conflicting results is that the populations in these studies differed in some important aspect. Because we excluded each individual with regular medication, none of our female subjects were taking estrogen or other hormonal therapy. No information about the use of drugs was given in the other studies.^{12,14,24} Of importance, animal studies have shown that both gonadectomy and sex hormone therapy can alter LV diastolic performance.²⁶ Our hypothesis is that the sex difference in LV filling in the middle-aged could be related to the effects of female menopause, but we admit that there may be other factors than hormonal status, not studied by us, that differentiate men from women in this age period.

Body mass index: Body mass index had an independent though small effect on each Doppler variable except the peak atrial velocity. With increasing index (i.e., with increasing overweight), the variables of the early diastolic flow were consistently reduced, whereas atrial filling fraction and relaxation time were increased. A novel finding, this suggests that even non-morbid obesity may impair LV diastolic function.

Heart rate and blood pressure: Heart rate had a relatively small influence on Doppler indexes in our total study population. Nevertheless, with increasing contraction frequency, the peak atrial velocity, atrial filling fraction and peak filling rate increased, whereas the peak velocity ratio and relaxation time decreased. The effect was most prominent in the youngest age group.

Systolic blood pressure had no independent effect on the Doppler indexes even though it showed modest correlations with them in univariate analyses. Diastolic blood pressure was somewhat more important in this respect, with a higher pressure being associated with a shift of filling to late diastole. The insensitivity of the Doppler filling indexes to blood pressure is a constant finding in several studies as well: neither Takenaka et al¹⁸ nor Smith et al²⁷ found any changes in the peak diastolic velocities at the time of marked acute elevations of blood pressure in healthy persons. Nevertheless, altered peak velocity ratio is a frequent finding in chronic hypertension.¹

Left ventricular size, mass and function, and left atrial size: Apart from the weak inverse relation between LV mass and peak filling rate, none of the other LV or left atrial measurements had an independent effect on Doppler indexes in the total study group. Neither have previous studies in healthy subjects shown any effect on Doppler indexes of LV end-diastolic di-

ameter,^{16,28} mass¹⁶ or fractional shortening.¹⁶ The radius/thickness ratio of the left ventricle also had no effect in healthy persons.¹¹ Altogether, these data suggest that in a normal population the Doppler filling indexes reflect the myocardial diastolic properties more closely than the gross structure of the left side of the heart. Nevertheless, in our middle-aged subjects both fractional shortening and end-diastolic diameter had an effect on the Doppler measurements. This is difficult to explain and must be addressed in future studies.

Physical activity and alcohol: Regular physical activity was associated with a favorable change in early LV filling in our subjects. This was most conspicuous in the elderly, in whom physical activity had a strong positive effect on the peak early velocity and early to atrial peak velocity ratio. A similar finding has previously been reported both in highly trained young athletes^{29,30} and in older runners compared with sedentary control subjects,³¹ but none of these studies adjusted for either the lower heart rate or the smaller body mass index in the physically trained subjects.

Regular use of alcohol at least twice a week, in contrast to occasional drinking and total abstinence, had an independent increasing effect on the peak filling rate and a decreasing effect on the atrial filling fraction, peak atrial velocity and relaxation time in our study group. This pattern of changes is compatible with a favorable change in LV relaxation.⁶⁻⁸ The alternative explanation, an increase in left atrial pressure, is extremely unlikely in our healthy and asymptomatic nonheavy drinking subjects. We have previously shown that chronic excessive drinking impairs the early filling indexes and prolongs the relaxation time,³² whereas a modest acute alcohol intake has little effect in healthy persons.²¹ Altogether, these data lead us to the provocative idea that alcohol could have a 2-faced influence on LV filling: favorable when used regularly in moderation but deleterious if abused. We strongly emphasize, however, that the statistical associations we report do not move causal relations. Rather, they should be seen as a source of hypotheses for further research.

Smoking did not appear as a major determinant of the Doppler indexes in our study. However, our group was not large enough to measure its true influence since there were only 3, 6 and 5 smokers among the young, middle-aged and old subjects, respectively.

Methodologic limitations: Because we studied healthy volunteers, we could not include invasive hemodynamic measurements in our analyses. The lack of data on left atrial pressure, an important determinant of Doppler indexes,^{6,17} appears particularly serious. However, the fact that our subjects were free of heart disease and thus probably had a narrow range of resting left atrial pressure clearly mitigates this limitation. The associations we report are based on interindividual

variation in the basal resting state. Our findings are therefore not directly applicable to changes in Doppler indexes in serial studies, e.g., after a medical intervention. The health of our subjects was based on a clinical and noninvasive appraisal. Exercise testing to detect occult coronary artery disease was not performed because its yield was expected to be relatively low in an asymptomatic group with few risk factors. Of importance, all subjects had normal and symmetric LV contraction on 2-dimensional echocardiography just before the Doppler study.

Practical implications: Considering clinical work, we think that the effect of any explanatory factor contributing >10% to the variation of the Doppler measurements should be considered in the interpretation of individual data. The effect of age could be taken into account in part by comparing individual measurements to normal values separately in the young, middle-aged and old persons (Table III). Regarding the early to atrial peak velocity ratio, the clinician should then also adjust for the effects of age and heart rate in the young, sex in the middle-aged, and physical activity as well as diastolic blood pressure in the elderly (Table V). Because of the strong confounding effect of left atrial pressure,^{6,17} conclusions about LV diastolic function should be made only after pulmonary congestion (or dehydration) has been corrected as fully as possible. This may appear a complicated procedure, but no solution is simple and reliable at the same time. Much more work is needed to augment the clinical use of Doppler filling indexes, lest they remain only prolific research tools.

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Bivariate Genetic Analysis of Left Ventricular Mass and Weight in Pubertal Twins (The Medical College of Virginia Twin Study)

Henri A. Verhaaren, MD, Richard M. Schieken, MD, Michael Mosteller, PhD,
John K. Hewitt, PhD, Lindon J. Eaves, PhD, DSc, and Walter E. Nance, MD, PhD

Left ventricular (LV) hypertrophy in adults is a recognized risk factor for the subsequent development of cardiovascular morbidity. To make informed preventive health decisions it is important to understand the interaction of genes and environment on LV mass. In both children and adults, weight is a strong correlate of LV mass. We hypothesized that genetic influences common to both of these variables could in part explain the strong relation between weight and LV mass in children. In a population of 341 twins (11 years old), these questions were asked: (1) How much of the total variance of LV mass is under genetic control? (2) After accounting for weight and weight adjusted for sexual maturity, how much of the remaining variance is genetic? (3) Of the total genetic variance, what proportion is specific for LV mass and what proportion is common to both weight and LV mass? (4) How much of the correlation between these 2 variables is explained by genes common to both LV mass and weight? Univariate genetic analyses documented that genes operating at different magnitudes in boys (63%) and girls (71%) explain a significant proportion of the variance of LV mass. After removing the effect of weight and sexual maturity by regression methods, genes remain an important influence. Bivariate genetic analyses confirmed that genes common to LV mass and weight significantly influence the covariation of these variables and that >90% of the correlation of LV mass and weight is due to common genes.

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Left ventricular (LV) hypertrophy assessed by echocardiography has been established to be both a consequence of hypertension and a more sensitive predictor for the subsequent development of coronary artery heart disease in adults.^{1,2} Increased LV mass, determined echocardiographically, was associated with all cardiovascular events occurring in both the original Framingham cohort and their offspring.³ This relation persisted after adjustment for age, diastolic blood pressure, treatment for systemic hypertension, cigarette smoking, diabetes mellitus, obesity, lipid abnormalities and electrocardiographic evidence of LV hypertrophy. In the elderly Framingham cohort, similar findings were observed for the predictive power of LV mass.⁴

In adults of all ages, Gardin et al⁵ found weight to be positively correlated with LV mass. In children as well, LV mass is closely correlated with measures of body size, such as weight and body surface area.^{6,7} Although the dimensions of cardiac wall thickness and chamber diameter in children do not vary linearly with body surface area, the echocardiographic assessment of LV mass does vary exponentially with body surface area.⁸ Among the school age children participating in the Muscatine study, body size measures accounted for 14% of the variability of LV mass.⁹

In a study of adult twins who had been reared apart, genetic influences on body mass index were found to be substantial and childhood environment to have little or no influence.¹⁰ Other genetic epidemiologic studies of body size in children using either twins or adopted sibships have found important genetic influences for LV mass and body size.^{11,12} In children, weight is under strong genetic control. Bodurtha et al,¹³ in a study of school age twins, found that genes accounted for 90% of the variability of weight.

Recently preventive measures are being advocated which are aimed toward prophylactically reducing LV mass.¹⁴ To make correct, informed preventive decisions it is important to understand the scientific basis for regulation of LV mass. Because of the known association of weight and LV mass, we hypothesized that genetic influences common to both variables in part could explain these findings. In a population of early pubertal

twins, we asked the following questions: (1) How much of the total variance of LV mass was under genetic control? (2) After accounting for weight and sexual maturity, how much of the remaining variance was genetic? (3) Of the total genetic variance, what proportion was specific for LV mass and what proportion was common to both LV mass and weight? (4) What proportion of the correlation between LV mass and weight was explained by genes common to both?

METHODS

Patient population: We ascertained 341 twin pairs living in the Commonwealth of Virginia using school rosters for identification. Descriptions of our study were sent by the school to the families and affirmatively replying families were invited to participate. All twins were examined as close as possible to their eleventh birthdays. Within the total population of 341 twin pairs, there were 254 caucasian twin pairs that made

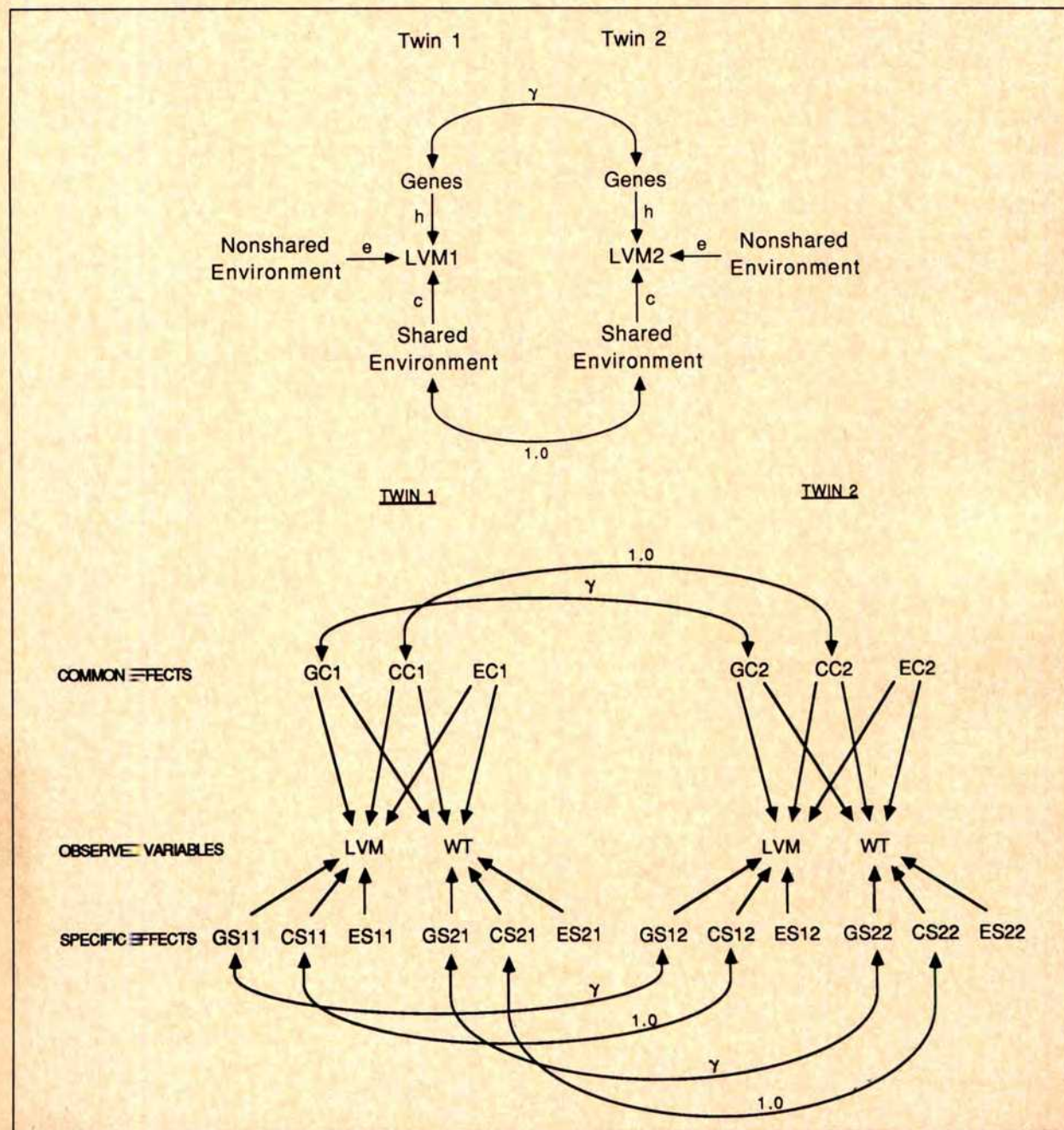


FIGURE 1. Illustrative path diagram. Model of left ventricular mass (LVM) being caused by genetic effects, and shared and non-shared environmental effects. h, c and e denote the magnitude of the genetic, and nonshared and shared environmental effects, respectively. γ denotes the correlation of the genetic effects between the 2 twins. $\gamma = 1$ if the twins are monozygotic. $\gamma = 0.5$ if the twins are dizygotic. The correlation of the environments shared by cotwins is fixed at 1.0. Bottom, full bivariate genetic model. WT = weight.

up the sample for this study. For the purposes of analysis, these 254 twin pairs were divided into 5 groups by zygosity and sex type. The designation twin 1 or twin 2 was by birth order except in the case of twins of the opposite sex where male twins were designated twin 1. The average age was 11.2 ± 0.2 years.

Zygosity determination: Zygosity was assessed by a questionnaire and confirmed by testing of the twins and their parents for the ABO, MNS, Rh, Kell, Fy, Hp, Tf, Hb, PGM, AP, G-6-PD, Ct and LDH systems. HLA typing was also performed. With this battery of polymorphisms, the probability of dizygosity for concordant pairs typically is <0.001 .¹⁵

Tanner stage: Pubertal staging of all children was performed using a 5-scale score based on Tanner's criteria.¹⁶

Echocardiography: Echocardiographic dimensions were measured according to standardized criteria from the mean values of 3 cycles.¹⁷ Cardiac dimensions were measured using a digitizing tablet and the values stored in ASCII files. Test-retest reliability with repeated measures of subjects and repeated digitizing of dimensions achieved an intraclass correlation of 0.92.

LV mass was calculated using the Penn convention where: $LV \text{ mass (g)} = 1.04 [(D_d + PW + VS)^3 - D_d^3] - 13.6$, where D_d is the LV diastolic dimension, PW is the wall and VS is the ventricular septum. This equation permits an estimate of LV mass by assuming that the ventricle is an ellipsoid during end diastole.¹⁸

Statistical analyses: DESCRIPTIVE STATISTICS: Mean differences within twin pairs were tested with a paired t test, male-female differences with a pooled t test. To summarize the twin-twin correlation by zygosity, correlation coefficients by sextype within zygosity group were pooled using a z-score procedure developed by Fisher.¹⁹ This procedure includes a test for the homogeneity of the correlation coefficients. A natural log transformation was used to normalize the distributions of weight and LV mass, both of which were positively skewed. To examine the extent of assortative mating, we examined spousal correlations for weight and body mass index.

UNIVARIATE GENETIC ANALYSIS: Our use of path analytic techniques for univariate genetic analyses has been described in previous publications.^{13,20} Causal hypotheses are represented as path diagrams in which observed variables are proposed as being determined by specified but unmeasured causes, such as genes and environment (Figure 1). The inclusion of opposite sex twins allows an estimate of sex specific genetic or environmental influences, or both. Lower correlations between opposite sex versus same sex dizygotic twins suggest different influences on boys than on girls (indicated by "h" and "e," respectively, in Figure 1). The path analysis quan-

TABLE 1 Mean \pm Standard Error of Left Ventricular Mass and Weight by Zygosity and Sex of Twins, Probability Level for Paired t Test Comparing Twin 1 with Twin 2, and Number of Twin Pairs for Each Group

		LV Mass (g)		Weight (kg)	
		Twin 1	Twin 2	Twin 1	Twin 2
Monozygotic twins					
Male-male	Mean	96.7	96.3	35.9	35.6
	\pm SEM	± 2.1	± 1.9	± 0.8	± 0.7
	p Value	0.81		0.43	
	No.	73		73	
Female-female	Mean	87.1	88.3	35.9	35.3
	\pm SEM	± 2.3	± 2.3	± 0.9	± 0.9
	p Value	0.47		0.12	
	No.	74		74	
Dizygotic twins					
Male-male	Mean	103.7	98.4	38.6	38.5
	\pm SEM	± 5.2	± 4.2	± 2.2	± 1.6
	p Value	0.22		0.95	
	No.	23		23	
Female-female	Mean	93.9	88.8	39.9	39.1
	\pm SEM	± 3.9	± 4.3	± 1.5	± 1.6
	p Value	0.25		0.59	
	No.	30		30	
Male-female	Mean	99.2	93.6	36.9	39.5
	\pm SEM	± 2.5	± 2.9	± 1.0	± 1.2
	p Value	0.12		0.06	
	No.	54		54	
SEM = standard error of the mean					

titates these differences. To formally test for sex difference, the chi-square of the model, genes and nonshared environment, (he) is compared to the chi-square of the model that allows for different magnitudes of genetic effects for boys and girls (hh'e). These models assume random mating with respect to LV mass and weight, no gene-environment interaction, no dominance or epistatic effects, and that monozygotic and dizygotic twins share environments to the same degree.

The LISREL VI program²¹ was used to obtain maximal likelihood estimates of model parameters and a chi-square goodness-of-fit statistic. Pairwise comparisons of alternative models were performed. The simplest model that adequately explained the data was selected as the best one.²² To assess the genetic effects on LV mass after removing both the genetic and environmental effects of weight and sexual maturity, we first regressed LV mass on weight and on weight plus Tanner stage. We performed a univariate genetic analysis on each of the resulting residuals.

BIVARIATE GENETIC ANALYSIS: We performed bivariate path analysis to investigate the nature of the interrelations between the genetic and environmental determinants of LV mass and weight. The effects included in the bivariate models were labeled as specific or common (see Appendix I). Specific effects are those that influence only 1 of the 2 variables, LV mass or weight. Common effects are those that influence both variables,

TABLE II Pearson Product-Moment Correlations, Pooled Correlations, Numbers of Twin Pairs, and Test Results for Homogeneity of Correlations

		Across Twins		Within Twins		Across Twin—Across Variable	
No. of Subjects		LVM1-LVM2	WT1-WT2	LVM1-WT1	LVM2-WT2	LVM1-WT2	WT1-LVM2
Monozygotic twins							
Male-male	73	0.59	0.86	0.58	0.54	0.48	0.52
Female-female	74	0.71	0.89	0.62	0.69	0.60	0.61
Pooled		0.66	0.88	0.60	0.62	0.54	0.57
p Value*		0.21	0.45	0.71	0.15	0.31	0.43
Dizygotic twins							
Male-male	23	0.56	0.41	0.77	0.68	0.27	0.66
Female-female	30	0.42	0.62	0.66	0.50	0.32	0.50
Male-female	54	0.17	0.33	0.61	0.57	0.14	0.18
Pooled		0.33	0.44	0.66	0.58	0.22	0.39
p Value*		0.18	0.27	0.50	0.63	0.70	0.05

*p value associated with the null hypothesis that all the pooled correlation coefficients are equal.
LVM1 = left ventricular mass twin 1; LVM2 = left ventricular mass twin 2; WT1 = weight twin 1; WT2 = weight twin 2.

TABLE III Results of Univariate Genetic Analysis*

"Best" Model Parameter	LV Mass (h ² e)		LV Mass on WT, Tanner Residuals (h ² e)	
	Estimate	SEM	Estimate	SEM
Males				
Genetic (h ²)	59.9%	10.4%	39.3%	10.1%
Shared env. (e ²)	0.0%	0.0%	0.0%	0.0%
Nonshared env. (e ²)	40.1%	4.5%	60.7%	6.7%
Females				
Genetic (h ²)	73.3%	10.3%	59.2%	10.1%
Shared env. (e ²)	0.0%	0.0%	0.0%	0.0%
Nonshared env. (e ²)	26.7%	3.0%	40.8%	4.5%
Goodness of fit tests				
Chi-square	6.66		6.54	
df	12		12	
p Value	0.88		0.89	
Common environment test				
Chi-square	0.0		0.0	
df	1		1	
p Value	1.00		1.00	
Sex differences test				
Chi-square	8.37		8.84	
df	1		1	
p Value	<0.01		<0.01	

h², c², and e² denote the components of variation due to genetic effects, and shared and nonshared environmental effects, respectively.
df = degrees of freedom; LV = left ventricular; env. = environment; SEM = standard error of the mean; WT = weight.

LV mass and weight. These effects were categorized further as genetic, nonshared environmental, or shared environmental. Shared environmental effects are those affecting both members of a twin pair. Measurement error is included in the nonshared environmental effects.

To answer the question, what proportion of the genetic effects on LV mass are common to LV mass and weight, a model was formulated in which all of the genetic and environmental effects that influence weight are assumed to affect LV mass (see Appendix II). This model²³ allows a partitioning of the variance into genet-

ic and environmental effects that are either specific for LV mass or common to both LV mass and weight. In addition, this model (see Appendix III) can be used to partition the correlation of LV mass and weight into genetic and environmental components.²⁴

RESULTS

Means: Table I presents a comparison of the untransformed LV mass and weight by zygosity and sex. The results are presented as mean \pm standard error of the mean. When pooled, the boys had greater LV mass than the girls (98.0 ± 1.2 vs 89.8 ± 1.3 g; $p < 0.01$). When compared with monozygotic twins, dizygotic twins had both greater LV mass (96.0 ± 1.5 vs 92.1 ± 1.1 g; $p < 0.03$) and weight (38.6 ± 0.8 vs 35.7 ± 0.4 kg; $p < 0.01$). By Tanner staging, the girls (2.14 ± 0.06) were more sexually mature than the boys (1.70 ± 0.04 ; $p < 0.01$).

Correlations: To explore the extent of assortative mating, spousal correlations for weight and body mass index were examined. We found no significant spousal correlation for either weight ($r = 0.08$; $p = 0.28$) or body mass index ($r = 0.10$; $p = 0.16$).

The Pearson product-moment correlation coefficients appear in Table II, by zygosity and sex type group for all of the variable-twin combinations. After pooling by sex type, the across twin monozygotic coefficients were larger than the across twin dizygotic coefficients for both variables, suggesting that genetic effects make a significant contribution to the observed variation. The pooled correlation coefficients within individual twins for LV mass and weight resulted in a large correlation ($r = 0.62$), suggesting that a sizable proportion ($r^2 = 38.4\%$) of the variation in LV mass could be accounted for by variation in weight. The across twin-across variable correlations provide insight into the possible sources of covariation between LV mass and weight. The pooled correlations for the monozygotic

pairs were higher than those for the dizygotic pairs, which may indicate that genetic effects are important in explaining covariation between the 2 variables.

Univariate analyses: Table III presents the best models for the univariate analyses of unadjusted LV mass and the residuals of LV mass on weight and Tanner stage. The regression of LV mass on weight was significant ($r^2 = 35.3\%$, $p < 0.0001$). No significant

differences were found for the univariate genetic analysis of the residuals of weight or the residuals of weight and Tanner stage. The model presents the parameter estimates of the residuals of weight and Tanner stage. In both cases (unadjusted and adjusted LV mass), a model that included genetic effects of different magnitudes in male (59.9%) and female (73.3%) twins and nonshared environmental effects was the most appro-

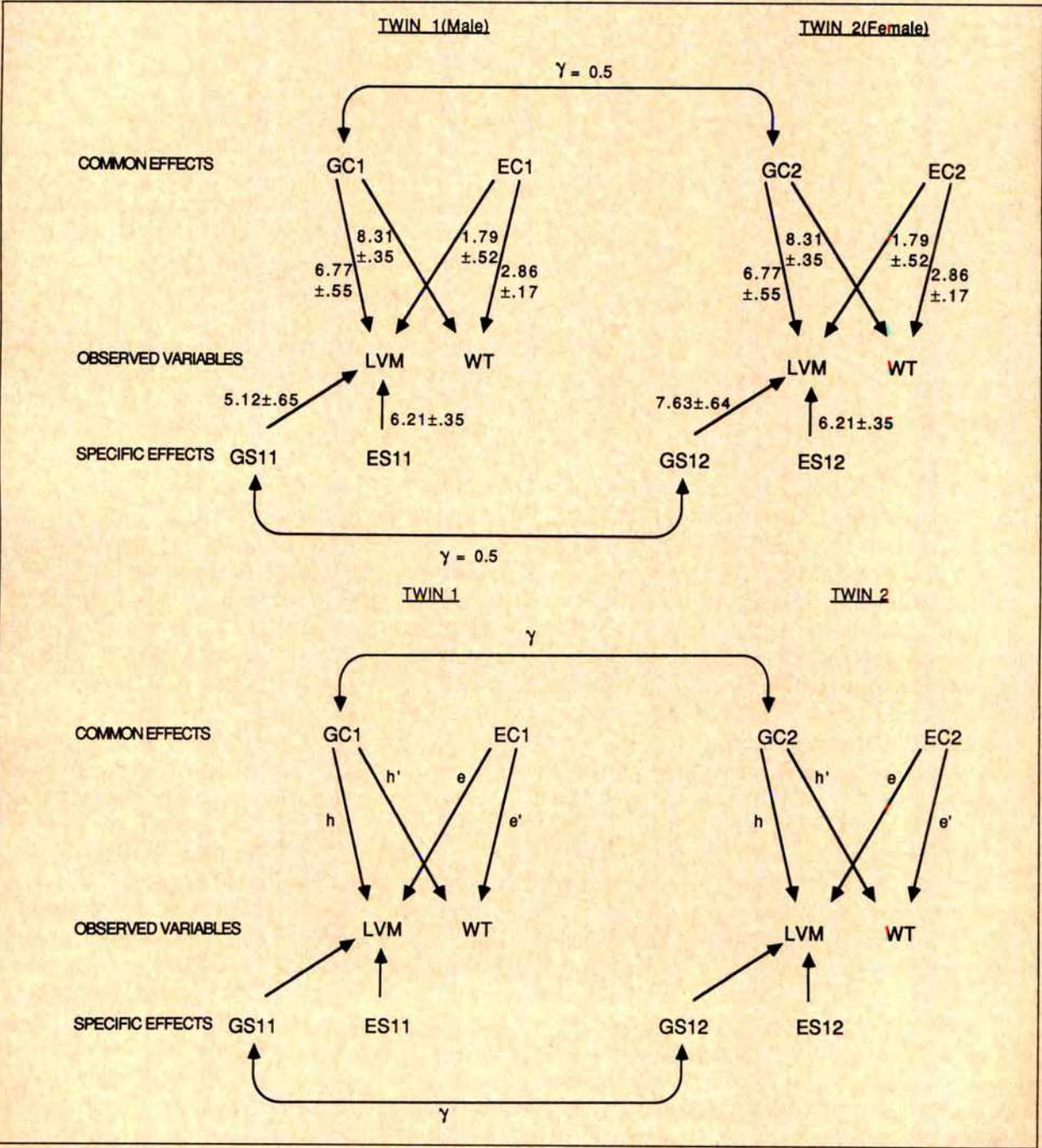


FIGURE 2. The best-fitting reduced bivariate model, with parameter estimates and standard errors. The best model did not include any shared environmental effects. *Bottom*, alternate form of bivariate genetic model. For simplicity, nonshared environmental effects are not shown. GC_j = genetic effect common to both variables in twin j (j = 1,2); EC_j = nonshared environmental effect common to both variables in twin j; GS1_j = genetic effect specific to left ventricular mass (LVM) in twin j; ES1_j = nonshared environmental effect specific to LV mass in twin j; WT = weight.

TABLE IV Estimates of Percentages of Variation in Left Ventricular Mass due to Genetic and Environmental Effects

		Percentage of Variance	
Source	Variance	Within Source (%)	Overall (%)
Boys			
Genetic effects			
Specific to LV mass	26.19	36	23
Common to LV mass and weight	45.89	64	40
Total genetic	72.08	100	63
Nonshared environmental effects			
Specific to LV mass	38.50	92	34
Common to LV mass and weight	3.22	8	3
Total nonshared environmental	41.72	100	37
Total	113.80		100
Girls			
Genetic effects			
Specific to LV mass	58.16	56	40
Common to LV mass and weight	45.89	44	31
Total genetic	104.05	100	71
Nonshared environmental effects			
Specific to LV mass	38.50	92	27
Common to LV mass and weight	3.22	8	2
Total nonshared environmental	41.72	100	29
Total	145.77		100

LV = left ventricular

LV = left ventricular.

priate. Neither model detected shared environmental effects. The percentage of the variance of LV mass attributed to genes is higher in the analysis of unadjusted LV mass than in the analysis of the residuals.

Bivariate genetic analyses: The best-fitting bivariate model (goodness of fit chi-square = 25.0; 40 degrees of freedom; $p = 0.97$), with parameter estimates, is depicted in Figure 2. The magnitudes of all the effects were equal in male and female subjects with the exception of the specific genetic effects on LV mass, which were slightly higher in female subjects. The model in which the specific genetic effects were constrained to be equal in boys and girls (chi-square = 31.8; 41 degrees of freedom; $p = 0.85$) fit less well. The difference in the 2 chi-squares was 6.8 with 1 degree of freedom, which was highly significant. We therefore rejected the hypothesis that the magnitudes of the effect in boys and girls were equal.

Table IV is a tabulation of the variance of LV mass partitioned according to source, based on the best-fitting model. Genetic effects accounted for >60% of the variance of LV mass in both boys and girls. The overall impact of genetic effects was slightly higher in girls than in boys. The genetic effects in boys were, for the most part, due to effects common to LV mass and weight, whereas in girls specific effects predominated. Environmental effects were almost exclusively those specific to LV mass (92%) rather than those common to LV mass and weight (8%).

With use of results from the best-fitting bivariate model, the correlation between LV mass and weight was partitioned into 2 components: the correlation due to common genetic effects and that due to the environmental effects common to the 2 variables. The genetic component of the correlation was 91.7%, and the environmental component of the correlation was 8.3%. These results provide a framework for understanding the covariation, within an individual, of LV mass and weight.

DISCUSSION

School age children who were persistently in the upper quintile of the blood pressure distribution for their age and sex had LV mass measurements that were beyond the expectation for their weight.⁹ In contrast, for children in the middle and lowest quintiles of the blood pressure distribution, LV mass was as expected for weight. In a recent study of the predictors of systolic blood pressure in children, weight and LV mass were highly correlated.²⁵

Adams et al,²⁶ using 1-way analysis of variance methods of Bouchard et al,¹¹ found familial influences on echocardiographic LV mass in college age students that included shared environmental plus genetic factors. They stated that further studies were necessary to fully characterize the specific contributions made by environmental or genetic factors, or both.

In black young adult twins, both before and after adjustment for body size, the intrapair variance of LV mass was higher for dizygotic than for monozygotic twins.²⁷ Regression analyses were performed using sex, systolic blood pressure and age as predictors of LV mass. In each instance the intrapair differences were greater for dizygotic twins. The investigators concluded that both genetic and environmental factors are important determinants of LV mass in blacks and that the influences are independent of sex, blood pressure and age.

In a study of 6- to 8-year-old twin children, LV mass correlated significantly with weight.²⁸ In addition, the intrapair variance of LV mass and LV mass adjusted for weight and sex was higher for dizygotic than for monozygotic twins. These observations strongly suggest that genetic influences are important in the variance of LV mass in children and that these factors may differ in boys and girls. However, the sample size of their study precluded the use of maximal likelihood analyses that would quantitate the variance into genetic and environmental contributions.

Bivariate path analytic techniques, which have been used in the genetic epidemiologic analysis of variables such as blood pressure and weight, offer the advantage of quantitative assignment of genetic and environmental variance.²⁹ This study, to our knowledge, is the first

to utilize path analysis to estimate the bivariate genetic and environmental components that are common to both weight and LV mass. It profits from design features that include a large sample of early pubertal twins of both sexes and same age. Our study was performed only in white children because we detected racial heterogeneity in the genetic regulation of LV mass. Unfortunately at this time our sample of black children is not large enough to adequately perform path analysis by race.

To understand more fully the relations of LV mass to weight, we began by studying the overall contribution of genes toward regulating the size of the left heart. Our study documents the following: (1) Genes account for $\geq 60\%$ of the total variance of LV mass in early pubertal children; (2) no shared environmental factors contribute to the variance; and (3) the magnitude of genetic effects is different in boys than in girls.

Importantly, the Tanner stages of sexual maturity showed that the girls were more advanced than the boys. The difference in sexual maturity may be partly reflected in weight because the addition of Tanner stage to the regression of LV mass did not alter the subsequent univariate genetic analysis of the residuals. Longitudinal genetic studies of these children as they enter young adulthood may help to determine the effects of puberty on LV mass. As the boys enter more advanced puberty, their estimated heritability of LV mass may increase to equal the heritability estimate of the girls. This would imply that different genes operate in childhood and adulthood and that there are no sex-determined LV mass heritability differences in adulthood. On the other hand, boys and girls may become less alike as they mature, suggesting that in adulthood different genes operate in each sex.

Previous work confirms that weight is under strong genetic influence in children.¹³ In univariate analysis, genes strongly influence weight and strongly influence LV mass. We chose to further analyze the genetic and environmental components of LV mass into specific effects on LV mass alone and the effects common to weight and LV mass.

A usual analytic procedure to understand a relation between 2 variables is to remove confounding relations by regression procedures. By regressing LV mass on weight and Tanner stage, we removed the direct phenotypic effects of weight and sexual maturity on LV mass. In so far as effects on variables such as height have effects on LV mass mediated through weight, adjustment of LV mass for weight will also remove these effects of height. Any direct effect of height not mediated through weight will still contribute to the specific genetic effects on LV mass. MacMahon et al³⁰ demonstrated a decrease in LV mass in middle aged, overweight, hypertensive patients treated with weight re-

duction. Daniels et al¹⁴ suggested that weight loss might reduce LV mass in children with persistently elevated blood pressure. Using the bivariate common factor model, we found that specific environmental influences common to weight and LV mass account for $<3\%$ of the total variability in children of both sexes. Based on our observation, the success of preventive interventions in normotensive children to decrease LV mass by moderate weight reduction may be limited.³¹ What effect weight loss might have on LV mass in obese hypertensive children is not known and warrants further study.

Importantly, this genetic analysis allows us to begin to understand the constant epidemiologic association of weight and LV mass. Over 90% of the correlation between these 2 variables in both boys and girls was explained by genes. The genes that control LV mass include both those specific to LV mass and those common to LV mass and weight. The genetic effects labeled "specific" for LV mass may include genes shared with other heritable variables such as blood pressure or heart rate. The bivariate analysis provides the basis for the initiation of multivariate models that can include both genetic and environmental variables to further define the mechanisms regulating LV mass.

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APPENDIX I

Full model for bivariate genetic analysis: The full bivariate path model used to explore the causal relation between LV mass and weight is shown in Figure 1, bottom. The observed or measured variables are LV mass (LVM) and weight (WT). The paths for both common effects and specific effects are illustrated. The unmeasured variables are: GC_j — the genetic effect common to both variables in twin j ($j = 1, 2$); CC_j — the shared environmental effect common to both variables in twin j ; EC_j — the nonshared environmental effect common to both variables in twin j ; GS_{ij} — the genetic effect specific to variable i ($i = 1, 2$) in twin j ($j = 1, 2$); CS_{ij} — the shared environmental effect specific to vari-

able i ($i = 1, 2$) in twin j ($j = 1, 2$); ES_{ij} — the nonshared environmental effect specific to variable i ($i = 1, 2$) in twin j ($j = 1, 2$).

APPENDIX II

Alternate formulation of the bivariate genetic model:

The reduced bivariate model in which weight (WT) is caused exclusively by effects common to both LV mass (LVM) and weight is shown in Figure 2, bottom. All effects of shared environment are omitted for simplicity. h denotes the magnitude of common genetic effects on LVM; h' denotes the magnitude of common genetic effects on WT; e denotes the magnitude of common nonshared environmental effects on LVM; e' denotes the magnitude of common nonshared environmental effects on WT.

APPENDIX III

Partitioning the left ventricular mass-weight correlation:

The correlation between LV mass (LVM) and weight (WT) is given by:

$$\begin{aligned} \text{Corr (LVM, WT)} &= \frac{\text{Cov(LVM, WT)}}{\sqrt{\text{Var(LVM) Var(WT)}}} \\ &= \frac{hh' + ee'}{\sqrt{\text{Var(LVM) Var(WT)}}} \\ &= \frac{hh'}{\sqrt{\text{Var(LVM) Var(WT)}}} + \frac{ee'}{\sqrt{\text{Var(LVM) Var(WT)}}} \end{aligned}$$

Thus, the component of the observed correlation due to genetic effects is:

$$\frac{hh'}{hh' + ee'}$$

and the component due to environmental effects is:

$$\frac{ee'}{hh' + ee'}$$

For LV mass and weight, the genetic component of the correlation was:

$$\begin{aligned} \frac{(6.77)(8.31)}{(6.77)(8.31) + (1.79)(2.86)} &= \frac{56.26}{56.26 + 5.12} \\ &= \frac{56.26}{61.37} = 91.7\% \end{aligned}$$

The environmental component of the correlation was:

$$\begin{aligned} \frac{(1.79)(2.86)}{(6.77)(8.31) + (1.79)(2.86)} &= \frac{5.12}{56.26 + 5.12} \\ &= \frac{5.12}{61.37} = 8.3\% \end{aligned}$$

Left Ventricular Ejection Fraction Measured with Doppler Color Flow Mapping Techniques

A. Resai Bengur, MD, A. Rebecca Snider, MD, Roger P. Vermilion, MD, and John C. Freeland

To determine if left ventricular (LV) ejection fraction (EF) can be accurately measured from the color Doppler examination, 11 patients (aged 0.4 to 22 years) underwent 2-dimensional and color Doppler examinations within 24 hours of cardiac catheterization. With use of a biplane Simpson's rule, LV end-diastolic volume, end-systolic volume and EF were measured from cineangiograms, 2-dimensional echocardiograms and color Doppler examinations. The 2-dimensional echocardiographic and color Doppler measurements were obtained from apical 4-chamber and long-axis views. The color Doppler examinations were performed by placing the color sector over the left ventricle only. The velocity scale was set at the lowest possible Nyquist limit (<0.17 m/s), and the highest possible carrier frequency was used to obtain this limit. With these settings, all flow signals in the LV chamber were aliased so that the entire chamber was filled with mosaic color Doppler signals. Motion of the surrounding LV walls gave rise to nonaliased (pure red-blue) signals. With use of an off-line analysis system equipped with a color frame grabber, the border of the mosaic color flow area was traced to obtain volumes and EF. End-diastolic and end-systolic volumes measured with color Doppler correlated well with those measured from 2-dimensional echocardiography ($r = 0.99$, standard error of the estimate [SEE] = 11.9 ml; $r = 0.99$, SEE = 4.4 ml, respectively) and cineangiography ($r = 0.92$, SEE = 16.8 ml; $r = 0.90$, SEE = 9.9 ml, respectively). Similarly, EF derived from color Doppler correlated extremely well with that measured from 2-dimensional echocardiography ($r = 0.99$, SEE = 1.6%) and cineangiography ($r = 0.96$, SEE = 3.4%). Thus, EF can be accurately measured from the color Doppler examination. With the addition of automatic edge-detecting al-

gorithms, this technique has the potential for providing a quick and automatic on-line calculation of EF.

(Am J Cardiol 1991;68:669-673)

In the management of patients with congenital and acquired heart disease, the ejection fraction (EF) is a commonly used and important index of left ventricular (LV) systolic function. Two-dimensional echocardiographic measurements of EF have correlated well with cineangiographic measurements of EF in children and adults.¹⁻⁵ However, for the measurement of EF, 2-dimensional echocardiography has several limitations. First, the 2-dimensional echocardiographic technique is time-consuming and cumbersome, requiring either the use of an off-line analysis system or the loss of time on the echocardiographic equipment for on-line analysis. Second, with 2-dimensional echocardiography, the endocardial borders of the left ventricle are often poorly visualized, making manual tracing methods very difficult and the development of automatic edge-detection methods, thus far, not possible. Because Doppler color flow mapping allows visualization of blood flow in the heart, we hypothesized that this technique could be used to enhance the distinction between the ventricular walls and blood pool and, thus, measure the ventricular volumes and EF with greater ease and accuracy. The purpose of this study was to determine the accuracy of ventricular volumes and EF derived from manual tracings of the color Doppler images compared with those derived from 2-dimensional echocardiography and cineangiography.

METHODS

Patients: Eleven patients undergoing echocardiographic examination and cardiac catheterization between September 1989 and April 1990 were randomly selected for inclusion in the study. Their ages ranged from 4.5 months to 22 years (mean 11) and their weights ranged from 7.3 to 70.6 kg (mean 35.3). The study group included 3 patients with pulmonary valve stenosis, 3 with aortic valve stenosis, 1 with supraaortic aortic stenosis, 1 with pulmonary atresia and a ventricular septal defect, 1 with coarctation of the aorta

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after a ventricular septal defect repair, 1 with dilated cardiomyopathy and 1 with mitral stenosis with a prosthetic mitral valve. Patients with abnormal ventricular shapes that did not conform to Simpson's rule (i.e., univentricular heart, absence of the majority of the ventricular septum) were excluded from the study.

Echocardiographic examination: Two-dimensional and color Doppler examinations were performed within 24 hours of cardiac catheterization using a 128-element phased-array ultrasound system (Acuson). The echocardiographic images were obtained from the apical 4-chamber and long-axis views. After recording the B-mode images, the color sector was positioned to include the entire left ventricle and exclude as much of the surrounding cardiac chambers as possible. The velocity scale of the color Doppler display was then decreased until all color Doppler signals arising from blood flow in the LV cavity were aliased and filled the chamber with

mosaic color Doppler signals, and all color Doppler signals arising from ventricular wall motion were displayed as nonaliased (pure red-blue) signals (Figure 1). Over the range of patient sizes, and heart and flow rates investigated, this required a Nyquist limit that was usually >0.08 m/s but always <0.17 m/s. On the ultrasound system we used, it was necessary to use the highest possible Doppler carrier frequency in order to obtain these low Nyquist settings.

Cardiac catheterization: At the time of cardiac catheterization, biplane LV cineangiography was performed in the left anterior oblique and 30° right anterior oblique projections. Although angiograms were obtained in all patients in the study, 3 patients had angiograms that could not be analyzed because of the absence of any sinus beats. The cineangiograms were transferred to $\frac{1}{2}$ -inch videotape for later off-line analysis.

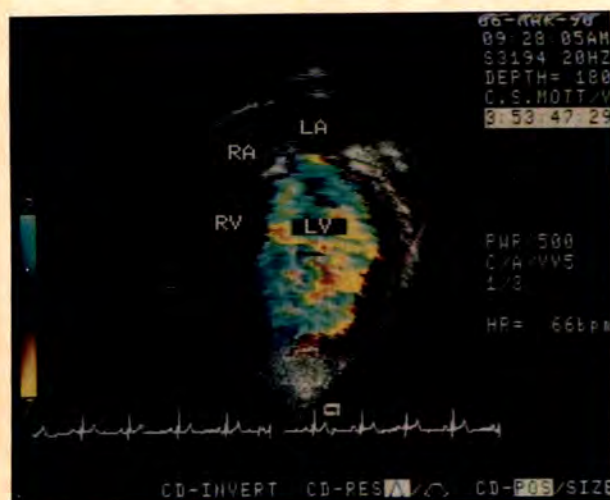


FIGURE 1. Color Doppler images at end-diastole (left) and end-systole (right) showing the technique used to determine left ventricular ejection fraction. The color sector is placed so as to include the entire left ventricle (LV), and the velocity scale has been decreased to the lowest possible setting. Note that the left ventricular cavity is filled with aliased (mosaic) color Doppler signals, whereas color Doppler signals arising from the left ventricular walls are pure red-blue (nonaliased). LA = left atrium; RA = right atrium; RV = right ventricle.

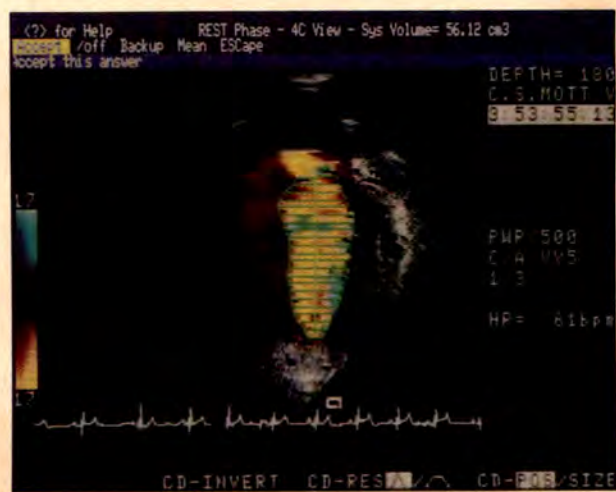
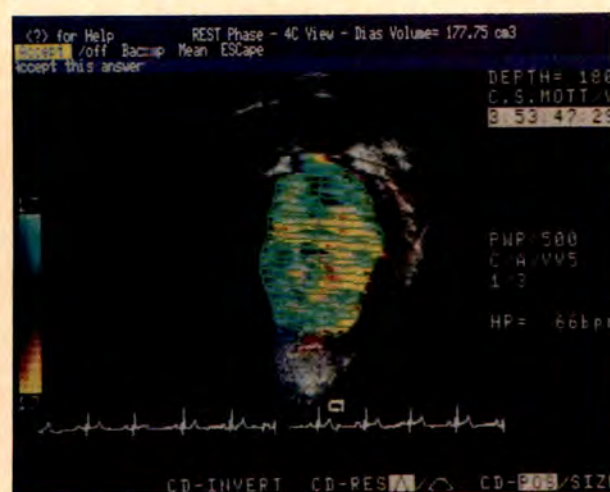


FIGURE 2. Color Doppler images at end-diastole (left) and end-systole (right) showing the technique used to calculate left ventricular volumes. The border of the color Doppler signals filling the left ventricle (mosaic signals) was manually traced (green line). The computer program then applied a Simpson's rule algorithm to calculate left ventricular volumes and ejection fraction.

Analysis: The echocardiograms and cineangiograms were analyzed by 2 observers who had no knowledge of the results of the other technique. All images were analyzed on a commercially available off-line analysis system equipped with a color frame grabber and software programs for biplane volume analysis (Freeland Medical System). For the color Doppler images, the outer margin of the mosaic flow area was traced manually at end-diastole and end-systole (Figure 2). The 2-dimensional and cineangiographic images were also digitized and traced along the endocardial border using the off-line system.

End-diastolic and end-systolic volumes and EF were calculated using a Simpson's rule method and paired biplane data for each measurement. For all the echo-

cardiographic and color Doppler studies, 3 cardiac cycles were measured and averaged. For the cineangiograms, 3 cardiac cycles were measured when available. With use of linear regression analysis, volumes and EF obtained from color Doppler were compared with those obtained from 2-dimensional echocardiography and cineangiography.

RESULTS

Figure 3 shows the comparisons of end-diastolic volumes measured from color Doppler with those measured from 2-dimensional echocardiography and cineangiography. For both comparisons, there was an excellent correlation ($r = 0.99$, $SEE = 11.9$ ml, and $r = 0.92$, $SEE = 16.8$ ml, respectively). Although end-

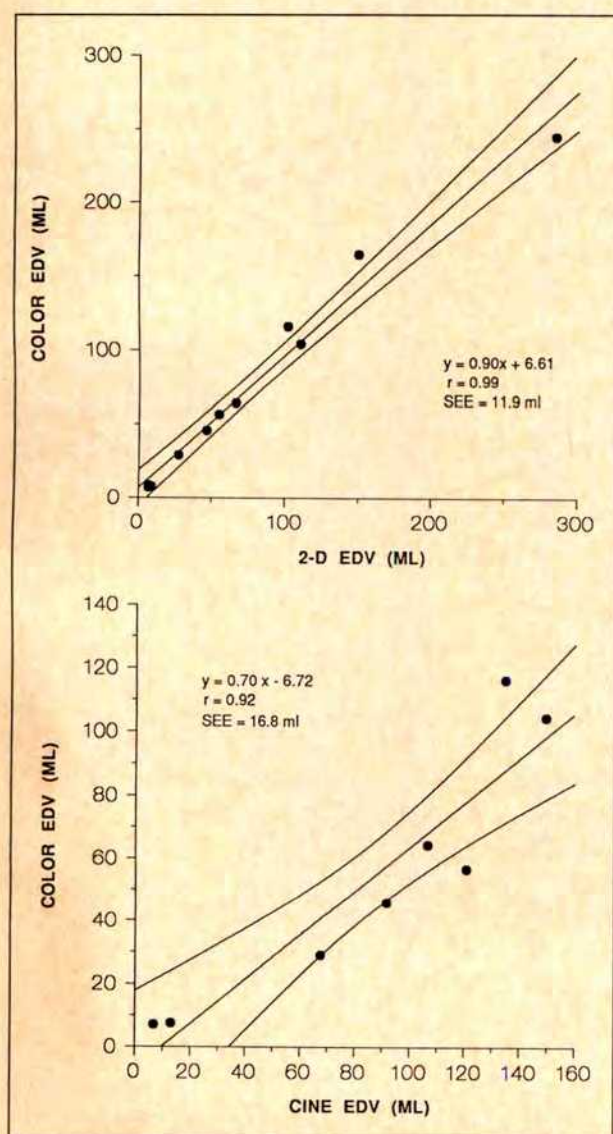


FIGURE 3. Correlation between left ventricular end-diastolic volumes (EDV) measured from color Doppler and those measured from 2-dimensional (2-D) echocardiography (*top*) and cineangiography (CINE) (*bottom*). Additional lines represent the 5 and 95% confidence limits. SEE = standard error of the estimate.

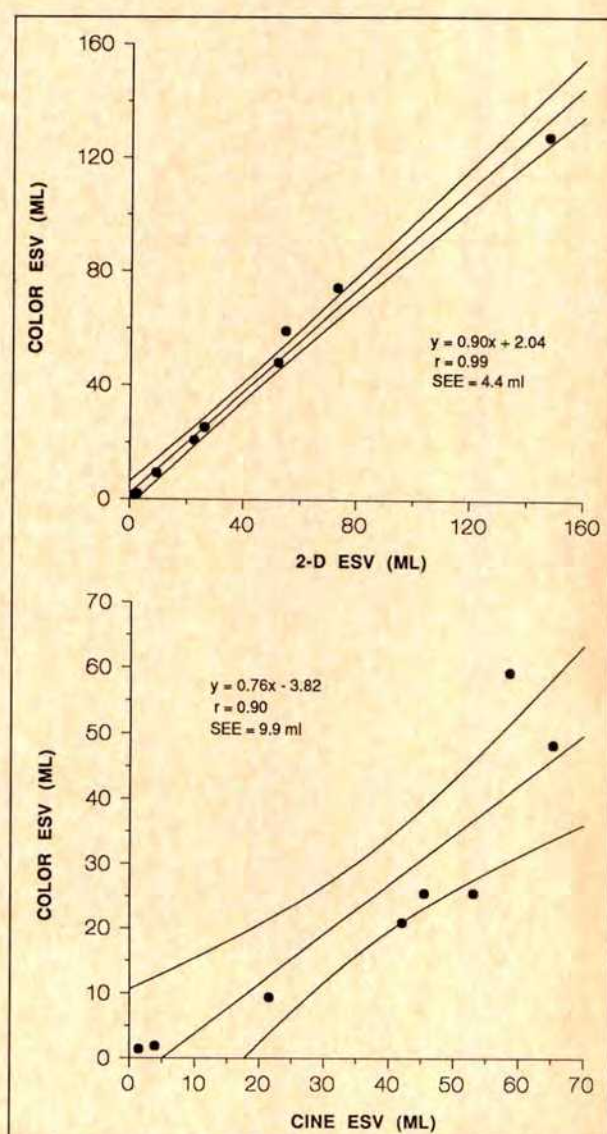


FIGURE 4. Correlation between left ventricular end-systolic volumes (ESV) measured from color Doppler and those measured from 2-dimensional (2-D) echocardiography (*top*) and cineangiography (CINE) (*bottom*). Additional lines represent the 5 and 95% confidence limits. SEE = standard error of the estimate.

diastolic volumes obtained using color Doppler and 2-dimensional echocardiography were nearly identical, the color Doppler technique tended to underestimate the end-diastolic volume obtained with cineangiography.

Similarly end-systolic volumes measured from color Doppler were nearly identical to those measured from 2-dimensional echocardiography (Figure 4). For the 2 techniques, $r = 0.99$ and $SEE = 4.4$ ml. As with end-diastolic volumes, the end-systolic volumes obtained from color Doppler tended to underestimate those obtained from cineangiography (Figure 4). For these 2 techniques, $r = 0.90$ and $SEE = 9.9$ ml.

Figure 5 shows the excellent correlation found between EF calculated from color Doppler and EF calcu-

lated from 2-dimensional echocardiography ($r = 0.99$, $SEE = 1.6\%$) and cineangiography ($r = 0.96$, $SEE = 3.4\%$). For both comparisons, EF obtained using the color Doppler technique tended to be slightly higher.

DISCUSSION

In this study, LV volumes and EF measured from manual tracings of Doppler color flow images correlated well with those measured from 2-dimensional echocardiography and cineangiography. Color Doppler and 2-dimensional echocardiographic results were nearly identical; however, volumes measured from color Doppler tended to underestimate those obtained from cineangiography. A similar trend has been observed when 2-dimensional echocardiographic volumes have been compared with cineangiographic volumes.² It is likely that catheterization volumes tend to be larger because of angiographic contrast filling of trabecular inter-spaces. The results of these comparisons highlight a limitation of the present study—i.e., the lack of a suitable reference standard to which the color Doppler data can be compared. Comparisons of echocardiographic and cineangiographic results have several “built in” sources of error that cannot usually be eliminated in the study design. Among these are lack of simultaneity of the studies and technical differences such as differences in the imaging planes, differences in sampling rates, and differences in image resolution. For future use of the color Doppler technique, it is extremely encouraging that the 2 noninvasive techniques yielded nearly identical results.

Although the 2-dimensional echocardiographic and color Doppler studies were obtained nearly simultaneously, with the same equipment, and in the same imaging planes, 1 major difference between the 2 techniques was the sampling rate or frame rate. On the 2-dimensional echocardiographic examinations, sampling rates were usually between 30 and 40 frames/s; however, on the color Doppler examinations, sampling rates were often as low as 15 frames/s. This could potentially result in an inability to identify precisely end-systole and end-diastole and, thus, should be a more important source of error in examining pediatric patients with rapid heart rates. For the color Doppler technique, we recommend that the color Doppler equipment be set so that color frame rates ranging from 15 to 25 frames/s are obtained.

The patients in this study were all children or young adults with EF ranging from 47 to 80%. We did not examine any technically difficult adult patients with low EF or apical aneurysms in which flow velocities may be extremely low. One anticipated problem with these adult patients is that, at the depths required to obtain their apical views, the velocity scale of the equipment may not have a low enough setting to allow alias-

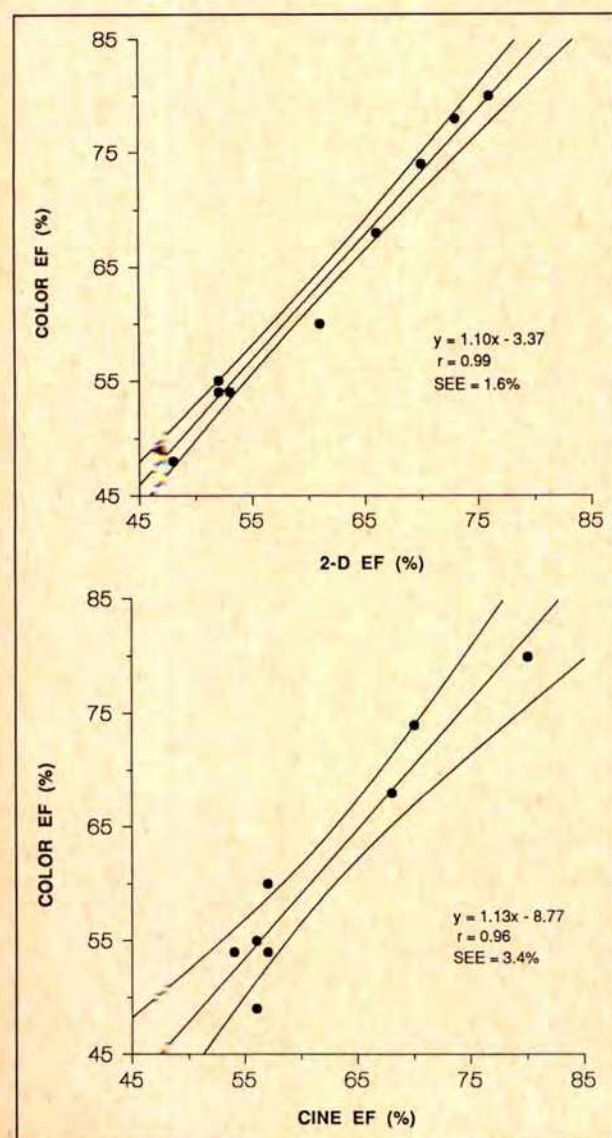


FIGURE 5. Correlation between left ventricular ejection fractions (EF) measured from color Doppler and those measured from 2-dimensional (2-D) echocardiography (top) and cineangiography (CINE) (bottom). Additional lines represent the 5 and 95% confidence limits. SEE = standard error of the estimate.

ing of color Doppler signals in the cardiac apex; or, even if the velocity scale can be set low enough, color Doppler signals from wall motion might also be aliased, causing confusion in recognizing the border between the cavity and the walls. Since this study was completed, we have successfully examined several young adult patients with dilated cardiomyopathy and EFs in the range of 20% using the color Doppler technique; however, studies in large numbers of technically difficult adult patients are necessary to determine the usefulness and limitations of the color Doppler technique in these patients. If necessary, the current Doppler equipment could be modified by the manufacturers in order to examine difficult adult patients. For example, the velocity scale and wall filters of the equipment could be modified or color Doppler power and velocity information may be combined to delineate better the boundary between the LV cavity and walls.

In patients with poor-quality 2-dimensional echocardiographic imaging, the color Doppler technique may enhance the distinction between the endocardial borders and blood pool and, thus, improve our ability to determine the boundaries of the LV cavity. In addition, the color Doppler technique may be extremely impor-

tant in the future development of technology for the automatic, on-line calculation of LVEF.

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Dipyridamole Sesta MIBI Myocardial Imaging

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Technetium-99m MIBI (hexakis-2-methoxy-2-methylpropyl-isonitrile) has recently been approved by the Food and Drug Administration for myocardial imaging in the U.S.A. Like thallium-201, it is a positively charged particle, but its transmembrane transport is not dependent on adenosine triphosphatase. It is highly lipophilic with 18 methyl groups, which may explain its ready transport across cellular membranes. Once inside the cells, it is, for the most part (84%), irreversibly bound to cytosol proteins. Like thallium-201, its regional uptake is dependent on coronary blood flow and myocardial viability; however, its retention is longer and its extraction rate lower than that of thallium-201. Sesta MIBI has a higher energy range (140 vs 70 KeV) and a much larger dose (15 to 25 vs 3 mCi) than thallium-201. Because of negligible redistribution, rest and stress images require 2 separate studies performed either on the same day (1-day protocol) or on 2 different days (2-day protocol). Image quality is superb and very suitable for single-photon emission computed tomography (SPECT). SPECT further enhances the diagnostic reliability of sesta MIBI studies by improving image contrast and avoiding overlap between normal and abnormal areas. Attenuation artifacts are less common and the images can be gated to assess regional wall motion and myocardial thickening. Alternatively, left ventricular function studies can be obtained simultaneously with the perfusion studies using first-pass radionuclide angiography.¹⁻⁶

Studies during treadmill exercise testing have shown a good agreement between thallium and sesta MIBI results. These studies were done in institutions with extensive experience in interpreting thallium results, which may have biased the results toward thallium. In the case of less experienced interpreters, results with sesta MIBI imaging are probably better than those with thallium imaging.²⁻⁵

With exercise testing, patients with coronary artery disease who only achieve a submaximal level of exercise generally have a lower sensitivity than those who achieve an adequate level of exercise.⁷ Pharmacologic

stress testing, using either intravenous dipyridamole or intravenous adenosine paired with thallium-201, has been of tremendous value in evaluating patients who either cannot exercise or cannot achieve a good level of exercise. Dipyridamole increases the endogenous adenosine concentration. Adenosine is a powerful coronary vasodilator; a dose of 140 $\mu\text{g/kg/min}$ causes coronary hyperemia comparable to that achieved with intracoronary papaverine, but unlike papaverine, adenosine is shorter acting and does not prolong the QT interval or produce ventricular arrhythmias.⁸⁻¹⁰

The degree of coronary hyperemia is probably higher with adenosine than with dipyridamole, using comparable doses; the hemodynamic effect is shorter in duration with adenosine, and submaximal hyperemic responses are probably more frequent with dipyridamole. It may be that a dose 50% higher than the currently recommended dose (0.56 mg/kg) produces coronary hyperemia that is comparable to that achieved with adenosine, but this issue has not been adequately tested.

One concern using sesta MIBI with pharmacologic testing is that at high-flow rates, the regional concentration of sesta MIBI may be considerably lower than the regional flow because of the decrease in extraction fraction as the flow increases. This may have an important implication in the detection of moderate stenosis. In this issue of *The American Journal of Cardiology*, Kettunen et al,¹¹ using a dose of 0.7 mg/kg of dipyridamole, found that the degree of coronary stenosis was significantly lower in arteries with a normal perfusion pattern than in those with an abnormal perfusion pattern (76 vs 82%, $p < 0.01$). In that study, the sensitivity of sesta MIBI imaging, using the high dipyridamole dose, was 95% in 42 patients with angiographically proven coronary artery disease. Furthermore, 78% of 92 diseased coronary arteries were correctly identified. Of 75 segments that were involved with perfusion defects, 68% were reversible, suggesting underlying ischemia. In a subgroup of 21 patients who also had thallium studies, 83% of diseased coronary arteries were correctly identified by sesta MIBI and 76% by thallium ($p =$ not significant), and there were 36 perfusion defects on sesta MIBI images and 37 on thallium images ($p =$ not significant). This high sensitivity with high-dose dipyridamole sesta MIBI imaging is very similar to our experience using adenosine with SPECT-thallium imaging and is generally higher than the sensitivity achieved during exercise. However, Tartagni et al¹² re-

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ported a sensitivity of 100% in 30 patients with coronary artery disease using the standard dose of dipyridamole.

Special features of the study by Kettunen et al include the use of a high dose of dipyridamole, SPECT imaging and quantitative coronary angiography to assess the degree of coronary stenosis. However, their study has flaws; the patients were highly symptomatic and 62% of them had prior Q-wave myocardial infarction, there was no control group to determine specificity, and it is also not clear how these patients were selected and why dipyridamole testing was used instead of exercise testing. Of interest is that in 31 segments defined as being akinetic by contrast left ventriculography, only 22 (71%) had fixed MIBI defects, suggesting that in the remaining patients these segments contained viable myocardium despite the presence of akinesia. The fact that adverse effects were few despite the higher dose of dipyridamole is encouraging. The investigators appear to suspect that the use of the handgrip test prevented hypotension and related symptoms.

Though Kettunen et al's study provides important information concerning the use of sesta MIBI with pharmacologic testing, it raises several other questions that remain unanswered: Should high-dose dipyridamole be used in all patients? Should sesta MIBI imaging replace thallium-201? Should pharmacologic stress testing replace exercise testing? Which coronary vasodilators should be used, adenosine or dipyridamole? Should simultaneous assessment of wall motion be obtained in addition to perfusion information? The answers to these questions are not yet available, although there are already strong opinions on each of these issues. Future studies should be carefully designed to address these issues.

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Anatomy of the "Posterior Septal Space"

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In this issue, the group from Westmead Hospital in Sydney, Australia, describes the results of an extensive study in which the dimensions of the posterior septal space and its relation to the coronary sinus were quantitated in 48 cadaver hearts. As is typical of this group, the study was performed in a meticulous

and scholarly manner and reported in a clear and concise fashion. The article contains important information regarding the anatomic landmarks of the posterior septal space, information that is of importance to both electrophysiologists and arrhythmia surgeons involved in the treatment of supraventricular arrhythmias.

Because of the previous publication of what is now recognized to be erroneous or incomplete information, many misconceptions exist of exactly what constitutes the "posterior septal space" and some of these misconceptions have resulted directly in poor operative results

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for the patients with the Wolff-Parkinson-White syndrome in the past. The word "space" in the term posterior septal space does not refer to the atrial septum or to the ventricular septum. It refers to the space lying immediately above the posterior portion of the septum of the *ventricle*.

Why does such a space exist? It exists because of the difference in the thickness of the walls of the atria and ventricles. Because the atria are thin-walled structures and because they must connect to the cephalad portion of the annulus fibrosis (i.e., the valve annuli), they must physically *diverge posteriorly* as they follow their attachments along the mitral valve annulus (left atrium) or tricuspid annulus (right atrium). To convey the concept of this important anatomic arrangement of the posterior atria, this region of the heart has been referred to as the "buttocks of the atrium" (Boineau JP, personal communication). The ventricles also attach to the valve annuli, but because they are thick-walled structures, they do not diverge into 2 easily identifiable structures posteriorly as they follow their attachments along the 2 valve annuli. As a result, the muscle masses of the right and left ventricles are approximated for some distance posterior to the central fibrous body, forming the posterior portion of the ventricular septum. Since the atrial walls directly across the valve annuli from this posterior ventricular septum are not in contact with one another, having diverged posteriorly, a space is created immediately above the posterior portion of the ventricular septum. This space is filled with fat, the terminal portion of the coronary sinus, and occasionally, the artery to the atrioventricular node.

Thus, the posterior septal space is a 3-dimensional structure. Indeed, it has been likened to a toppled pyramid, with the apex of the pyramid at the central fibrous body and its base at the epicardial reflection covering the fat pad at the crux of the heart.¹ An accessory atrioventricular connection that courses through the fat occupying this posterior pyramidal space is referred to as a "posterior septal pathway," only because its *ventricular* end inserts into the cephalad portion of the posterior ventricular septum. This classification has nothing to do with the site of insertion of the atrial end of the pathway. In fact, many surgeons, including this reviewer, believe that the atrial end of the posterior septal pathways rarely if ever inserts into the true atrial septum, but rather that they attach to the posteromedial free wall of either the right or left atrium after these 2 structures have diverged posteriorly. The point becomes moot if one uses the endocardial surgical technique in which the fat pad is simply separated from the top of the posterior portion of ventricular septum, thus dividing only the ventricular end of the accessory pathway. However, it explains why the epicardial technique is successful in dividing the atrial end of these path-

ways, because with this approach, the fat pad in the posterior septal space is separated from the posteromedial walls of the right and left atria where they have diverged posteriorly. The true atrial septum, i.e., that portion of the atrial septum where no surgical plane exists between the right and left atrial walls, is not dissected using the epicardial technique, yet this surgical approach is nearly as successful in dividing "posterior septal pathways" as is the endocardial approach.

From a practical clinical standpoint, electrophysiologists and arrhythmia surgeons have had to develop a reasonable system of classifying the location of accessory pathways responsible for the Wolff-Parkinson-White syndrome. Under optimal circumstances, the anatomic classification should correlate with discriminatory electrophysiologic findings that characterize a given pathway as being located in a specific anatomic space. In this manner, the anatomic classification used to assist the surgeon is not entirely arbitrary. Fortunately, such a classification was established early in the course of surgery for the Wolff-Parkinson-White syndrome and it has proven infallible clinically in all but a few instances. However, this anatomic classification is based entirely on the potential sites of insertion of the ventricular ends of accessory pathways. Because of the anatomic peculiarities of the atria (mentioned previously), accessory pathways probably never connect to the true atrial septum. Thus, any anatomic classification based on *atrial* anatomy would preclude the classification of posterior septal or anterior septal accessory pathways. Left freewall, posterior septal, right freewall and anterior septal pathways all have definitive electrophysiologic characteristics that localize them to one of those specific anatomic spaces on the ventricular surface. The major exception is the so-called "paraseptal" accessory pathway that inserts into the ventricle at the somewhat arbitrary "junction" between the left free wall and the posterior portion of the ventricular septum.

As Davis et al state,² it is easy to categorize true posterior septal pathways and true left freewall pathways, but the "paraseptal" pathways in between are more perplexing. This fact is especially true during an endocardial electrophysiologic study or radiofrequency catheter ablation, or both, since the electrograms are recorded in this area from a coronary sinus catheter which is on the atrial side of the atrioventricular groove, yet the anatomic classification, as mentioned, is based on ventricular anatomy. Davis et al provided an important group of measurements that will undoubtedly be of great benefit to electrophysiologists who perform radiofrequency catheter ablation of accessory pathways in this region of the heart. The benefit of these measurements may extend to arrhythmia surgeons as well, but only if they understand the posterior septal space in all 3 of its dimensions.

Finally, from a purely surgical standpoint, I would point out an important inaccuracy in their anatomic description of the posterior septal space. This error in anatomic description is of no importance to successful catheter ablation, but it can (and has) resulted in the inadvertent creation of complete heart block when performing surgical dissection for posterior septal accessory pathways. Through no fault of theirs, published reports are replete with descriptions of the posterior septal space in which the terms "central fibrous body" and "right fibrous trigone" have been used interchangeably.^{3,4} Even the great pathologic anatomist, McAlpine,⁵ uses these terms interchangeably in his classic atlas. Regardless of what these structures are called, the fact exists that there is a fibrous structure between the mitral and tricuspid valves that is formed by the convergence of these 2 valve anuli. This fibrous structure (the central fibrous body) extends for varying distances posterior to the site at which the aortic valve anulus is contiguous with the mitral and tricuspid valve anuli, a site properly referred to as the right fibrous trigone. In other words, the right fibrous trigone is only the most anterior portion of the central fibrous body.

This seemingly inconsequential semantic point is of paramount importance to the arrhythmia surgeon. Although the precise location of the His bundle may vary slightly from patient to patient, the His bundle invariably penetrates the anatomic atrioventricular junction at a point *between* the right fibrous trigone and the most posterior extent of the central fibrous body. Therefore, when surgical dissection for posterior septal pathways is performed, all dissection should be confined to the space *posterior* to the central fibrous body and no portion of the central fibrous body should be exposed during the dissection. If this principle is not followed, inadvertent heart block will be created in a substantial number of patients. Of equal importance to surgical success is the fact that even those posterior ac-

cessory pathways that are closest to the His bundle invariably insert into the ventricle posterior to the central fibrous body. Therefore, the most posterior extent of the central fibrous body is the key anatomic structure that invariably separates the His bundle from posterior septal accessory pathways. By carrying the surgical dissection up to but not across the central fibrous body, accessory pathways located in this apex of the posterior septal space can be divided safely without fear of creating heart block.

As mentioned above, many articles and texts do not differentiate between the central fibrous body and the right fibrous trigone. Davis et al also make this mistake.² This error results in surgeons' believing that the dissection for posterior septal pathways should be continued anteriorly to the right fibrous trigone,^{1,3,4} a practice that results in inadvertent and preventable heart block in many patients. In contrast, adherence to surgical principles based on the accurate anatomy of the posterior septal space has resulted in the successful surgical division of 105 consecutive posterior septal accessory pathways in our series without a single instance of heart block without late recurrences during a 10-year follow-up period (unpublished data).

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Usefulness of Serum Creatinine as a Marker for Coronary Events in Elderly Patients with Either Systemic Hypertension or Diabetes Mellitus

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Elderly patients with systolic or diastolic hypertension,^{1,2} or with diabetes mellitus,^{1,2} have an increased incidence of new coronary events. Renal disease occurs in patients with systemic hypertension or diabetes mellitus. Some³⁻⁶ but not all studies^{7,8} have shown that patients on chronic maintenance dialysis have an increased incidence of mortality from cardiovascular disease. This article reports the results from a prospective study performed to correlate increased serum creatinine in elderly patients with systemic hypertension or diabetes mellitus with the incidence of new coronary events.

In a prospective study of 1,396 patients in a long-term health care facility, 532 (38%) had systolic or diastolic hypertension, 285 (20%) had diabetes mellitus, and 662 (47%) had systemic hypertension or diabetes mellitus. The 662 patients included 497 women and 165 men (mean age \pm standard deviation 82 ± 8 years, range 62 to 100). A systolic blood pressure of ≥ 160 mm Hg on 3 occasions was considered systolic hypertension.⁹ A diastolic blood pressure of ≥ 90 mm Hg on 3 occasions was considered diastolic hypertension.⁹ All patients with hypertension were treated during the study. Diabetes mellitus was diagnosed if the patient was receiving insulin or oral hypoglycemic drugs to control hyperglycemia, or if fasting venous plasma glucose levels were ≥ 140 mg/dl on 2 occasions. Serum creatinine ≥ 1.5 mg/dl on ≥ 2 occasions was considered increased.

Mean age was 81 ± 8 years in patients with increased serum creatinine and 82 ± 8 years in patients with normal serum creatinine ($p =$ not significant). Mean follow-up was 41 ± 21 months (range 3 to 73) in patients with increased serum creatinine and 42 ± 22 months (range 3 to 73) in patients with normal serum creatinine ($p =$ not significant). New coronary events were diagnosed if the patient developed myocardial infarction, primary ventricular fibrillation or sudden cardiac death. Myocardial infarction was diagnosed as previously described.¹⁰ Primary ventricular fibrillation was diagnosed as ventricular fibrillation documented by electrocardiogram in a clinically stable patient unexpectedly having new cardiac symptoms. Sudden cardiac death was defined as an unexpected cardiac death in a patient found dead within 1

hour of being clinically stable.¹¹ Chi-square analysis was used to analyze data.

Of 662 patients with systemic hypertension or diabetes mellitus, 184 (28%) had an increased serum creatinine. Table I shows the incidence of new coronary events in patients with systemic hypertension and no diabetes mellitus, in patients with systemic hypertension and diabetes mellitus, and in patients with diabetes mellitus and no hypertension. Table I also lists levels of statistical significance.

Lindner et al³ reported that cardiovascular disease was the most frequent cause of death in patients on maintenance hemodialysis for renal failure. Lazarus et al⁴ concluded that hypertension played a major role in the increased incidence of death from cardiovascular disease in uremic patients on chronic maintenance dialysis. Haire et al⁵ demonstrated that smoking and hypertension were significant risk factors for cardiovascular mortality in patients on maintenance dialysis for renal failure. Rostand et al⁶ found that diastolic hypertension contributed to hemodialysis-associated ischemic heart disease. Burke et al⁷ did not find that long-term dialysis accelerated atherosclerosis. Vincenti et al⁸ found that atherosclerosis may not be accelerated by hemodialysis and may be prevented by more careful control of hypertension.

Increased serum creatinine was present in 28% of our elderly patients with systemic hypertension or diabetes mellitus. The results from this study show that increased serum creatinine is associated with a higher incidence of coronary events in patients with systemic hypertension, with or without diabetes mellitus, but not in patients with diabetes mellitus without systemic hypertension. However, only 27 patients in this study had diabetes mellitus

TABLE I Association of Increased Serum Creatinine with New Coronary Events in Elderly Patients with Systemic Hypertension and Diabetes Mellitus

	Coronary Events			
	Increased Serum Creatinine		Normal Serum Creatinine	
	No.	%	No.	%
Hypertension without diabetes	60/99	61*	122/278	44
Hypertension with diabetes	42/58	72*	47/97	48
Diabetes without hypertension	13/27	48	42/103	41

* $p < 0.005$.

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without systemic hypertension and with increased serum creatinine. Therefore, increased serum creatinine is a marker for an increased incidence of coronary events in elderly patients with systemic hypertension, with or without diabetes mellitus, but not in elderly patients with diabetes mellitus without systemic hypertension.

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Usefulness of Placement of Intraoperative Epicardial Wires During Automatic Implantable Cardioverter-Defibrillator Insertion to Preclude the Need for Transvenous Catheters at the Predischarge Electrophysiology Study

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The management of ventricular tachyarrhythmias and sudden cardiac death has changed remarkably since the advent of the automatic implantable cardioverter-defibrillator (AICD).¹⁻⁶ In patients undergoing implantation of the AICD, postoperative testing is used to judge the efficacy of the device. In the past, the predischarge study has required placement of transvenous pacing catheters in order to induce clinical arrhythmias. We evaluated the reliability of induction of ventricular tachyarrhythmias in the postoperative period using temporary epicardial pacing wires placed during AICD implantation.

We studied 20 patients (14 men and 6 women), aged 35 to 81 years (mean 57 ± 14) who underwent AICD placement after electrophysiologic testing for evaluation of out-of-hospital cardiac arrest (6 of 20 [30%]), spontaneous sustained ventricular tachycardia (12 of 20 [60%]), symptomatic nonsustained ventricular tachycardia (1 of 20 [5%]) and near syncope (1 of 20 [5%]).

All patients underwent preoperative electrophysiologic testing after informed consent was obtained. Antiarrhythmic agents were discontinued ≥ 5 half-lives before testing. Multiple electrophysiology catheters

were placed in the high right atrium, His bundle position, right ventricular apex, and occasionally in the coronary sinus. Programmed atrial and ventricular stimulation was performed at twice diastolic threshold with a rectangular pulse width of 2.0 ms. Sustained monomorphic ventricular tachycardia was induced in 11 of 20 patients (55%), pleomorphic ventricular tachycardia or ventricular fibrillation was induced in 7 of 20 patients (35%), hemodynamically significant nonsustained ventricular tachycardia in 1 of 20 patients (5%), and 1 patient, who had out-of-hospital ventricular fibrillation, did not undergo preoperative electrophysiologic testing because of severe coronary artery disease. All patients had no successful results with 2.25 ± 1.8 antiarrhythmic regimens before placement of the AICD.

All patients underwent a standard midline sternotomy approach.⁵⁻⁷ Patients received 2 screw-in rate-sensing leads and 2 epicardial patch electrodes. Thirteen of 20 patients (65%) received 2 large patch electrodes (CPI model L67), whereas 7 (35%) received 1 large and 1 small (CPI model A67) patch electrode. Two to 3 temporary epicardial pacing wires were placed in the diaphragmatic wall of the myocardium (A and E medical M-26 orange temporary epicardial pacing wires) using a simple peel-back technique.⁸ Patients received the Ventak 1550 (13 of 20 [65%]), the Ventak 1600 (4 of 20 [20%]) or the Ventak 1510 (2

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TABLE I Patient Characteristics and Results of Electrophysiologic Testing

Pt. No.	Age (yr) Sex	Preop. Diagnosis	Preop. Induced Rhythm (ms)	Induction Mode	Termination	Postop. Induced Rhythm (ms)	Induction Mode
1	35 F	VT/VF	VF	S ₄ RVA	CV (320 J)	VF (200)	AC
2	40 M	OHVFA	Vflut (200) SMVT (240) Before proc.	S ₄		SMVT (215)	Burst
3	54 F	OHVFA	None with isuprel			VF (170)	AC
4	59 M	OHVFA	No baseline			VF (165)	Burst
5	60 M	OHVFA	VF	S ₅ RVA	Spontaneous	VF	AC
6	67 F	SMVT/VFA	SMVT (250) SMVT (231) After proc.	S ₄ CV 320J	Spontaneous	VF (180)	AC
7	69 M	VT/VF	Vflut	S ₄ RVA	CV (80J)	VF (205)	Burst
8	70 M	VT/VF	SMVT (320) SMVT (285) Before proc.	S ₃ RVA	S ₃ term.	SMVT (300)	S ₅
9	72 M	OHVFA	SMVT (316) SMVT (276) Before proc.	S ₃ RVA		SMVT (215)	Burst
10	37 F	SMVT	NSVT	S ₄		VF (150)	AC
11	38 M	SMVT	VF	S ₄ RVOT	CV (320 J)	VF (105)	AC
12	45 F	SMVT	VF	S ₄ RVOT	CV (320 J)	VF (140)	AC
13	50 M	SMVT	Vflut SMVT (230)	S ₃ RVOT CV 80J		SMVT (240)	AC
14	53 M	SMVT	SMVT	S ₃ RVOT		SMVT (333)	Burst
15	59 M	SMVT (350 ms)	SMVT (500)	S ₃	S ₃ term.	SMVT (270)	S ₄
16	65 M	SMVT	SMVT (300)	S ₃ RVA	CV	SMVT (290)	S ₄
17	69 M	SMVT	SMVT (353)	S ₃ RVA	CV (320 J)	SMVT (250)	Burst
18	81 F	SMVT	SMVT (240)	S ₃ SVA	CV (160 J)	VF (175)	AC
		DY9 p MI				SMVT (270)	AC
19	67 M	NSVT	SMVT (300)	S ₃	CV (240 J) SMVT (320 ms) SMVT (350 ms)	SMVT (350) S ₃ , AC S ₃ , AC	S ₃ , AC
20	42 M	Sync.	SMVT (343)	S ₃ RVOT	SMVT (235 ms) SMVT (225 ms)	SMVT (275) S ₃	S ₃

AC = alternating current; Burst = rapid ventricular pacing; CV = cardioversion, 80 to 360 J; DY9 p MI = day 9 after myocardial infarction; NSVT = nonsustained ventricular tachycardia; OHVFA = out-of-hospital ventricular fibrillation/cardiac arrest; postop. = postoperative; preop. = preoperative; proc. = procainamide 1.0 to 1.25 g given intravenously; RVA = right ventricular apex pacing site; RVOT = right ventricular outflow pacing site; S = extrastimulus after pacing at 600 or 400 ms for tachycardia induction, or during tachycardia for tachycardia termination; SMVT = sustained monomorphic ventricular tachycardia; Sync. = syncope; term. = termination; VF = ventricular fibrillation; VFA = ventricular fibrillation/cardiac arrest; Vflut = ventricular flutter, monomorphic, cycle length 200 to 220 ms; VT/VF = ventricular tachycardia/fibrillation.

of 20 [10%]), all manufactured by CPI. The Ventak 1600 was an investigational device at the time of this study. Three patients (15%) underwent combined coronary artery bypass surgery with placement of the AICD.

Patients underwent postoperative electrophysiologic testing using the epicardial wires 6.55 ± 2.9 days after implantation of the AICD. Nine of 20 patients (45%) underwent pacing in the bipolar mode, and 11 (55%) in the unipolar mode.

All patients had inducible sustained ventricular arrhythmias at postoperative electrophysiologic testing using the epicardial pacing electrodes. Nine of 20 patients (45%) required alternating current for induction, while burst pacing or programmed electrical stimulation up to S₅ were used in 11 patients (55%). Induction of arrhythmias was achieved with 8.66 ± 2.07 mA output, with a rectangular pulse width of 9.0 ± 2.6 ms. There was a good correlation between the presenting arrhythmia, the rhythm induced in the preoperative electrophysiologic test, and the rhythm in-

duced in the postoperative study (Table I). Patients tolerated this procedure well, with minimal discomfort during induction of arrhythmias. In all patients, the AICD recognized the arrhythmia, and converted the patient out of the arrhythmia on the first shock of 26.9 ± 7.3 J (range 6 to 31).

Seven of 20 (35%) of these patients were discharged from the hospital on the day of the postoperative electrophysiologic study, 2 (10%) were discharged on the subsequent day, and 10 were discharged 6.6 ± 3.6 days after electrophysiologic testing. The mean time to discharge after AICD testing was 3.3 ± 3.9 days.

Epicardial wires have been routinely used by cardiac surgeons in patients who have undergone coronary artery bypass surgery, congenital heart disease repair or valvular surgery, to treat postoperative rhythm disturbances, pace the heart during transient atrioventricular conduction delays, and improve the cardiac output in states of low flow relative to bradycardia.⁷⁻⁹ As a general rule, these leads are removed when the patient becomes sta-

ble after surgery. It is known that pacing thresholds increase after surgery with these electrodes.⁸ We used the technique described by Edgerton et al,⁹ which has been shown to result in a low incidence of cardiac arrhythmias, and retained foreign material at wire removal and a low incidence of threshold elevations during in situ pacing. We used these wires in the postoperative period for induction of ventricular arrhythmias in order to test the implanted defibrillator. This is a new application of an old technology, that reduces the risk of postoperative electrophysiologic testing, reduces patient discomfort associated with this procedure, and has the potential to shorten the hospital stay after implantation of the AICD.

Postoperative electrophysiologic testing is routinely performed after AICD implantation to check the efficacy of the device before discharge. This is currently performed by transcutaneous placement of quadripolar pacing catheters in the right ventricular apex through the femoral or antecubital veins. This carries attendant risks as described in a published report on electrophysiologic testing.¹⁰ Although for general electrophysiologic testing, the benefits clearly outweigh the risks, for postoperative electrophysiologic testing, techniques that reduce the need for invasive catheter placement would seem prudent in order to avoid these risks.

There were no complications associated with use of these epicardial wires for induction of ventricular tachyarrhythmias, nor any complications with removal of these wires. All patients had effective induction of tachycardia using acceptable stimulation energies. The implantable defibrillator recognized the tachycardia and

successfully converted the rhythm in all patients. Therefore, placement of epicardial pacing wires at the time of AICD implantation provides a safe and effective means of inducing clinical arrhythmias in postoperative electrophysiologic testing, without the need for transvenous catheter placement.

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Electrophysiologic Effects of Intravenous Propafenone at Rest, During Isoproterenol Infusion and During Exercise in the Wolff-Parkinson-White Syndrome

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Propafenone, a class Ic antiarrhythmic agent,¹ has been shown to be effective in restoring sinus rhythm in patients with symptomatic orthodromic tachycardia associated with Wolff-Parkinson-White syndrome (WPW).^{2,3} The high rate of conversion to sinus rhythm (>60%) is attributed to the relatively high dose administered (2 mg/kg). In addition, recurrence of tachycardia can be prevented in most cases. The effec-

tiveness of the antiarrhythmic agent is usually tested at rest. Information concerning the pharmacologic effects of drugs during exercise in patients with supraventricular arrhythmias is scarce. In this study, the electrophysiologic effects of propafenone were examined in 10 patients with WPW at rest, during isoproterenol infusion and during exercise to evaluate its antiarrhythmic properties under these conditions.

Ten male patients (mean age 32 years, range 17 to 46) with WPW were studied. All patients manifested anterograde conduction over the accessory pathway on the surface electrocardiogram at rest. They were studied because of palpitations, syncope or presyncope, and all were candidates for surgical cure of WPW.

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TABLE I Electrophysiologic Data

Pt. No.	Values	AH	HV	AERP	TCL	AV	VA
1	C	100	45	280	360	160	200
	P	130	45	310	450	200	250
	PI	80	45	290	320	125	195
	PE	80	45	310	345	140	205
2	C	90	45	220	NS		
	P	90	45	270	NS		
	PI	—	—	—	—		
	PE	95	45	245	NS		
3	C	120	50	300	NS		
	P	120	50	340	NS		
	PI	100	40	270	NS		
	PE	130	50	320	NS		
4	C	100	45	240	380	220	160
	P	110	50	240	390	215	175
	PI	80	45	200	270	120	150
	PE	90	45	220	340	160	180
5	C	80	40	280	NS		
	P	80	60	370	NS		
	PI	70	50	220	NS		
	PE	85	50	270	NS		
6	C	80	40	290	330	230	100
	P	70	90	Block	370	240	130
	PI	60	80	220	250	170	80
	PE	70	70	220	300	190	110
7	C	95	40	270	300	145	165
	P	100	60	260	340	160	180
	PI	70	50	210	270	100	170
	PE	95	50	230	300	130	170
8	C	70	40	380	NS		
	P	—	—	Block	NS		
	PI	—	—	Block	NS		
	PE	—	—	Block	NS		
9	C	80	45	260	420	270	150
	P	70	60	Block	440	260	180
	PI	70	50	220	290	150	140
	PE	70	50	220	320	150	170
10	C	140	35	270	320	190	130
	P	90	60	Block	NI		
	PI	70	35	230	250	140	110
	PE	70	35	Block	270	140	130

AERP = anterograde effective refractory period of accessory pathway; AV = anterograde conduction time during tachycardia; C = baseline values at rest; NI = not inducible; NS = not sustained; P = baseline values after propafenone infusion; PE = values on exercise after propafenone administration; PI = values after administration of isoproterenol and propafenone; TCL = cycle length of tachycardia; VA = retrograde conduction time during tachycardia.

In all patients, orthodromic tachycardia or atrial fibrillation had been documented before electrophysiologic evaluation. After having given informed consent, all patients underwent an electrophysiologic study without any oral medication. All medication was discontinued ≥ 5 half-lives before the study. No sedation was given before the study. Three to 5 multipolar electrodes were inserted through the right femoral vein and positioned in the right atrium, right ventricular apex, coronary sinus and across the tricuspid valve to record the His bundle potential. Four surface electrocardiogram leads (I, II, V_1 and V_6) were recorded simultaneously with the endocardial signals on a 16-channel ink-jet recorder (Mingograph, Siemens-Elema, Solna, Sweden). The anterograde refractory period of the accessory pathway was determined in

sinus rhythm and at 1 or 2 atrial pacing cycle lengths (600 or 500 ms). The atrioventricular (anterograde) conduction time (measured from the retrograde atrial depolarization and the first deflection of the QRS complex on the surface electrocardiogram) and ventriculoatrial (retrograde) conduction time (measured from the first deflection of the QRS complex and the retrograde atrial deflection) were determined at rest and during sustained orthodromic tachycardia when such arrhythmia was inducible with premature atrial or ventricular extrasystoles. The patients were studied in the supine position and the study was begun ≥ 30 minutes after introduction of the recording leads. A baseline electrophysiologic study was performed and orthodromic tachycardia was induced where possible. The characteristics of the tachycardia, such as anterograde and retrograde conduction times, were recorded. Atrial fibrillation was not induced during the baseline study. After the baseline study, intravenous propafenone was administered (1 mg/kg over 5 minutes). At five and 10 minutes after propafenone administration, electrophysiologic data were determined. Isoproterenol was then administered (1 to 6 $\mu\text{g}/\text{min}$) to increase heart rate to 120 to 140 beats/min, and the electrophysiologic characteristics of the accessory pathway were again determined. Isoproterenol was then stopped. When the heart rate returned to the baseline value, exercise was begun in the supine position using a cycloergometer at a charge of 100 W. The aim was to reach heart rates (± 10 beats/min) during exercise similar to those during isoproterenol infusion. After 3 minutes of exercise, a fourth evaluation of the electrophysiologic data was performed at a similar heart rate to that during isoproterenol infusion. Initiation of orthodromic supraventricular tachycardia was attempted at rest, after propafenone and isoproterenol infusions and during exercise. Tachycardia was stopped with programmed electrical stimulation. Data during tachycardia were analyzed only in patients with sustained supraventricular tachycardia during the various steps of the study. Plasma levels of propafenone were not determined. Data were expressed as mean \pm standard deviation. Statistical analysis was performed using a paired Student 2-tailed t test. A p value < 0.05 was considered significant. Electrophysiologic data are listed in Table I. In 4 patients, anterograde conduction was suppressed by propafenone, but resumed in 3 of the 4 patients after administration of isoproterenol. During exercise, complete anterograde block of the accessory pathway persisted in 2 patients after propafenone administration. In patients with a persistence of preexcitation after propafenone administration, the anterograde effective refractory period increased from 265

± 46 to 302 ± 46 ms ($p < 0.05$). In patients with preexcitation at rest, the anterograde effective refractory period decreased to 225 ± 31 ms during isoproterenol administration and to 254 ± 41 ms ($p < 0.05$) during exercise. These differences are also significant when compared with the resting values before and after administration of propafenone. Baseline AH interval changed only slightly from 95 ± 21 to 96 ± 21 ms ($p =$ not significant [NS]) after administration of propafenone. However, it decreased significantly during infusion of isoproterenol to 75 ± 12 ms ($p < 0.05$), but not during exercise (87 ± 19 ms, $p =$ NS). Baseline HV interval increased significantly from 43 ± 4 to 56 ± 15 ms ($p < 0.05$) after propafenone, but decreased after isoproterenol (49 ± 13 ms) and during exercise (49 ± 9 ms). In 6 patients, sustained orthodromic tachycardia was inducible at rest, during exercise, and after isoproterenol and propafenone administrations. In only 1 patient was orthodromic tachycardia not inducible after propafenone administration, but was inducible again after administration of isoproterenol and during exercise. In the 5 other patients, mean cycle length of tachycardia increased significantly from 352 ± 44 to 398 ± 47 ms ($p < 0.05$). Isoproterenol abolished the effect of propafenone as the cycle length of tachycardia decreased to 275 ± 27 ms ($p < 0.05$). During exercise, cycle length of tachycardia decreased to 312 ± 28 ms ($p < 0.05$). The baseline value of anterograde conduction did not increase significantly (202 ± 47 to 215 ± 38 ms; $p =$ NS) after administration of propafenone. Exercise and infusion of isoproterenol decreased atrioventricular conduction to 155 ± 29 ms and to 134 ± 25 ms ($p < 0.05$), respectively. Retrograde conduction time over the accessory pathway was significantly modified by the administration of propafenone and increased from a baseline value of 150 ± 34 to 183 ± 43 ms ($p < 0.05$). Infusion of isoproterenol and exercise decreased retrograde conduction time to 140 ± 41 ms and to 158 ± 41 ms ($p < 0.05$), respectively. Modifications in the anterograde refractory period of the accessory pathway, in the cycle length of tachycardia and in the anterograde and retrograde conduction times are represented in Figure 1. In 4 patients, oral propafenone therapy was performed without completely suppressing episodes of tachycardia. In the 6 remaining patients, surgical cure of WPW was performed during the same hospital stay. No adverse effects were reported by our patients despite relatively rapid administration.

The antiarrhythmic efficacy of propafenone has been extensively demonstrated in animals and humans.^{1,2} Ludmer et al³ reported significant prolongation of both the anterograde and retrograde refractory periods of ac-

cessory pathways in patients with WPW. These results were confirmed by Dubuc et al⁴ who demonstrated complete anterograde block in 6 of 15 patients and also significant prolongation of anterograde and retrograde conduction times of the accessory pathway. Our results confirm these observations. We noted significant modifications in the conduction of the accessory pathway after propafenone administration and complete anterograde block occurred in 4 of the 10 patients (patients 6, 8, 9 and 10). However, isoproterenol completely reversed the effect of propafenone by decreasing the refractory period of the accessory pathway; exercise induces the same reversal of the effect of propafenone on the refractory period of the accessory pathway, although not as significantly. During isoproterenol infusion and during exercise, the anterograde refractory period of the accessory pathway was shorter than during baseline. Furthermore, in 3 of these 4 patients (patients 6, 9 and 10), anterograde conduction resumed after isoproterenol and in 2 (patients 6 and 9) during exercise. In 6 patients (patients 1, 4, 6, 7, 9 and 10), sustained orthodromic tachycardia was inducible during the 4 different conditions. In only 1 patient (patient 10) was tachycardia not inducible at rest or after propafenone administration. This is less than the 82% of nonreinducibility of tachycardia after propafenone administration reported by Ludmer et al.³ Breithardt et al⁵ reported a completely or partially favorable response in 6 of 15 patients with orthodromic tachycardia. The lower dose of propafenone used in our study (1 mg/kg) compared with that used by Ludmer and Breithardt and their co-workers (2 mg/kg) may explain these differences. However, we noted a significant increase in the cycle length of tachycardia mainly due to modifications in the retrograde conduction properties of the accessory pathway. Exercise and infusion of isoproterenol significantly accelerated the cycle length of tachycardia mainly by

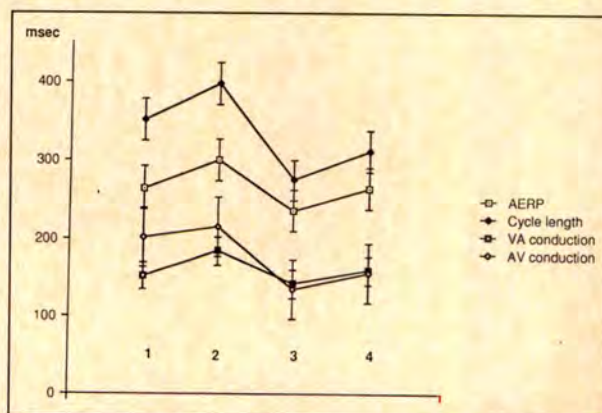


FIGURE 1. Variation of anterograde refractory period of the accessory pathway (AERP), cycle length of tachycardia, and anterograde (AV) and retrograde (VA) conduction times during orthodromic tachycardia. 1 = resting values; 2 = resting values after propafenone administration; 3 = values after isoproterenol infusion; 4 = values on exercise.

Urinary Kallikrein Excretion in Congestive Heart Failure

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The renal kallikrein-kinin system has been implicated in the control of local renal blood flow, salt and water excretion and blood pressure regulation.¹ Renal kallikrein is synthesized in the connecting tubule cells of the rat and human nephron. From here it may be secreted to the surrounding blood vessels or directly into the lumen of the tubule or to both.² Kallikrein releases kinins from plasma substrates called kininogens. Kinins are potent vasodilators and have natriuretic and diuretic properties.¹

Congestive heart failure (CHF) is characterized by an abnormal sodium and water retention and increased vascular resistance. The role of other vasoactive systems such as renin-angiotensin, prostaglandins and catecholamines has been extensively studied. However, there is no information regarding participation of the renal kallikrein-kinin system in CHF. We determined urinary kallikrein in patients with CHF in different functional classes and we analyzed its relation with indexes of renal function and with other vasoactive systems such as plasma renin activity and circulating catecholamines.

We studied 11 ambulatory patients with stable CHF in New York Heart Association class II to III (mean age \pm standard deviation 61 ± 2 years) (group A). These patients were taking digoxin 0.125 to 0.25 mg/day, diuretics (furosemide 40 to 80 mg/day) and potassium supplement (potassium chloride 16 to 32 mEq/day). In addition, we studied 6 patients with decompensated CHF in New York Heart Association class IV (mean age 50 ± 6 years), with pulmonary as well as visceral congestion and peripheral edema (group B). These patients had been admitted to the hospital and received the same treatment as the other group, but were receiving larger doses of diuretics. Vasodilators had been withdrawn during the week before the study. Sodium intake was restricted to 4 g/day in both groups. We excluded patients with present or past renal diseases. Ten normal subjects (mean age 39 ± 6 years) served as controls. Diuresis, urinary sodium and potassium and creatinine clearance were measured in all groups. In addition, plasma samples for determinations of plasma renin activity and noradrenaline levels were also taken in the supine posi-

tion after a resting period of 1 hour, and were determined according to previously reported techniques.³ Urinary kallikrein activity was estimated from a 24-hour collected urine sample by its amidolytic activity on the chromogenic tripeptide substrate H-D-Val-Leu-pNitroaniline, S-2266 (Kabi Diagnostica, Sweden).⁴ Each urine sample was dialyzed and assayed against his own blank containing aprotinin, and the kallikrein activity was expressed in units per 24 hours, 1 unit being the amount able to hydrolyze 1 μ mol of substrate per minute at 37°, pH 8.2. Anova and the Student-Newman-Keuls test for multiple comparisons were used to analyze differences between groups. Simple linear regression was used for correlation analysis. Data of controls and patients are listed in Table I.

Urinary kallikrein excretion was significantly lower in patients with CHF than in controls, and it decreased progressively according to the severity of CHF ($p < 0.01$). Creatinine clearance decreased progressively and significantly according to the severity of CHF ($p < 0.01$), although 24-hour diuresis was similar for all groups. Urinary sodium excretion was significantly higher in controls than in group A and B patients ($p < 0.01$), and urinary potassium excretion was significantly higher in controls than in group A patients ($p < 0.01$). No significant differences were found in plasma noradrenaline among the 3 groups, although the values tended to be higher in group B patients. Plasma renin activity increased significantly and progressively in patients with CHF ($p < 0.01$). Urinary kallikrein excretion values did not correlate with creatinine clearance, electrolytes, plasma renin activity or noradrenaline.

Because urinary kallikrein has been related to diuresis and natriuresis, our results suggest that decreased urinary kallikrein excretion observed in patients with CHF could be related to the abnormal sodium and water retention that characterizes this syndrome. Moreover, the excretion decreased according to the severity of CHF.

In the kidney, kallikrein is secreted in both the luminal and basolateral membranes of connecting tubule cells to the interstitial space,² where it may reach the intravascular compartment.⁵ Kallikrein released into the interstitial space could generate kinins, which in turn may affect renal hemodynamics.⁶ Furosemide is known to stimulate urinary kallikrein excretion.⁷ It is possible that urinary kallikrein levels determined in our patients could have been influenced by this drug. However, our patients in

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TABLE I Clinical and Physiologic Data of Control Subjects and Patients with Congestive Heart Failure

	NYHA Class	Etiol., Age (yr) & Sex	Diuresis (ml/24 hours)	Urinary Na (mEq/liter)	Urinary K (mEq/liter)	Creat. Clear. (ml/min)	PRA (ng/ml/hour)	Noradrenaline (pg/ml)	Urinary Kallikrein (U/24 hours)
Control Subjects									
1	—	29 M	1,240	158	70	149	1.7	247	774
2	—	64 M	650	84	38	122	1.6	888	356
3	—	18 M	740	189	75	128	0.4	217	1,861
4	—	18 M	750	130	29	141	0.8	297	956
5	—	33 M	2,400	239	86	138	1.1	243	1,836
6	—	64 F	2,150	264	70	145	0.4	418	970
7	—	21 F	750	168	40	130	0.2	350	1,224
8	—	27 F	800	124	26	143	0.4	352	1,912
9	—	52 F	660	95	38	104	0.3	504	460
10	—	66 F	2,310	200	77	145			905
Mean ± SEM		39 ± 6	1,245 ± 222	165 ± 19	55 ± 7	135 ± 4	0.8 ± 0.2	391 ± 65	1,125 ± 181
Group A									
1	II	IDC, 60 M	1,200	88	48	94	3.8	196	1,173
2	II	IDC, 63 M	1,560	80	24	90	2.2	522	440
3	II	IDC, 72 M	2,910	111	19	32	5.2	804	235
4	II	IDC, 58 M	2,480	117	21	70	0.9	564	659
5	II	IDC, 60 M	1,840	132	62	114	1.9	400	812
6	II	IDC, 63 M	1,250	106	19	97	4.8	536	373
7	II	IDC, 65 M	1,950	106	54	112	1.7	202	1,413
8	III	IDC, 59 F	1,500	73	20	90	2.6	660	430
9	III	IDC, 58 F	1,400	112	16	101	4.1	533	423
10	III	IDC, 46 F	2,200	74	15	45	8.6	499	1,018
11	III	IDC, 63 F	2,040	111	14	140	1.0	450	473
Mean ± SEM		61* ± 2	1,848 ± 162	101* ± 6	28* ± 5	90*† ± 9	3.3* ± 0.7	488 ± 51	677*† ± 109
Group B									
1	IV	IDC, 43 M	2,190	54	36	28	16.0	1,185	95
2	IV	IDC, 62 M	1,530	98	48	64	2.2	1,338	39
3	IV	IDC, 48 M	2,310	86	32	58	2.8	440	95
4	IV	IDC, 56 M	1,890	84	34	44	5.5	240	322
5	IV	IDC, 70 M	1,860	75	42	31	5.0	238	130
6	IV	IDC, 21 F	790	92	38	42	11.5	518	133
Mean ± SEM		50 ± 7	1,762 ± 205	82* ± 6	38 ± 2	45* ± 6	7.2* ± 2.2	660* ± 196	136* ± 40

* p < 0.01 versus control subjects; † p < 0.05 versus group B.

CAD = coronary artery disease; Creat. Clear. = creatinine clearance; Etiol. = etiology; IDC = idiopathic dilated cardiomyopathy; K = kallikrein; Na = sodium; NYHA = New York Heart Association; PRA = plasma renin activity; SEM = standard error of the mean.

functional class IV, who received the largest doses of furosemide, had the lowest urinary kallikrein values. This finding could indicate that this excretion is diminished to both the luminal and intravascular space. There is no information in published reports on the effect of digitalis on the kallikrein system.

It is possible that the low levels of urinary kallikrein found in our patients could contribute to further lower glomerular filtration rate by altering the vasomotor tone of the afferent or efferent arterioles.⁶

Decreased glomerular filtration rate could also be related to the highest levels of plasma renin activity observed in patients with most severe CHF. An increase of renin-angiotensin activity contributes to both peripheral and renal vasoconstriction, with further impairment of renal blood flow and glomerular filtration rate reduction.⁸ Urinary kallikrein may produce local vasodilation and aid in supporting renal blood flow even in the presence of high circulating levels of angiotensin II.¹ These intrarenal homeostatic mechanisms seem to be altered

in CHF, since the patients with highest plasma renin activity levels had the lowest urinary kallikrein values. Our findings in CHF are similar to those observed in patients with advanced cirrhosis of the liver, concomitant renal failure, high plasma renin activity and low urinary kallikrein values.⁹

Renal hypoperfusion has been related to decreased urinary kallikrein excretion.^{8,10} This could be the case in our patients in functional class IV. However, urinary kallikrein excretion was also decreased in patients with stable CHF who were in functional class II to III, with a normal glomerular filtration rate. Therefore, decreased urinary kallikrein excretion in CHF could be related not only to renal hypoperfusion, but also to part of an abnormal neurohormonal activation in CHF.

The relation between the adrenergic nervous system and kallikrein-kinin system has been recently explored. In an in vitro model, it was found that kallikrein release and its biosynthesis were inhibited by a β_1 adrenergic agonist.¹¹ It appears that the increased sympathetic tone

in the kidney inhibits the release of kallikrein into urine.¹² Decreased urinary kallikrein excretion found in our patients with CHF could be a consequence of increased sympathetic stimulation.

We evaluated the renal kallikrein-kinin system by urinary kallikrein measurements. Our data suggest that this intrarenal hormonal system involved in water and electrolyte excretion and renal blood flow regulation may be part of an abnormal neurohumoral axis in CHF.

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Comparison of Mitral Valve Area Results of Balloon Mitral Valvotomy Using the Inoue and Double Balloon Techniques

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Inoue pioneered the mitral balloon valvotomy technique using his homemade balloon catheter as a nonsurgical therapeutic alternative to the surgical treatment of mitral stenosis.¹ Because Inoue's balloon catheter was not commercially available at the time, Zaibag et al² developed the principal of the double balloon technique.² The double balloon technique has prevailed to date since the mitral valve areas achieved are excellent and are maintained at long-term follow-up.²⁻⁴ Although the mechanism of mitral valve dilatation for both the Inoue and the double balloon technique are similar,¹⁻⁵ i.e., commissural splitting, no comparative clinical data have been reported. Previous published series include noncomparable groups of patients, with different ages and particularly different mitral valve and subvalvular anatomy.¹⁻⁴ We selected a homogenous, young population of patients with severe rheumatic mitral stenosis; both groups of patients had comparable mitral valve and subvalvular anatomy and age. The objective of the study was to compare the mitral valve areas and the total procedure times achieved, using the 2 different techniques.

We selected 16 patients according to the following criteria: (1) severe symptomatic pliable mitral valve stenosis with a mitral valve area $<1.1 \text{ cm}^2$, (2) mitral

valve regurgitation $<\text{grade 1}$ (Sellers classification), (3) echocardiographic score ≤ 8 using the Block classification,⁶ and (4) absence of calcification of the mitral commissures. Nine patients were randomly assigned to group 1 for balloon valvotomy using 2 Mansfield balloon catheters (20 + 20 mm in diameter) and 9 patients to group 2 using the Inoue balloon technique with 26- to 30-mm balloon catheters.¹ Group 1 consisted of 5 men and 3 women (mean age \pm standard deviation 31 ± 11 years). Six patients were in New York Heart Association class II and 2 in class III. The mean age of the 8 patients (4 men and 4 women) in group 2 was 32 ± 11 years; 7 patients were in New York Heart Association class II and 1 in class III. All 16 patients were in sinus rhythm.

The double balloon mitral valvotomy technique, using 20 + 20-mm Mansfield balloon catheters, has been previously described and was performed in group 1 patients (Figure 1).^{2,3} In group 2 patients, mitral balloon valvotomy was performed using the Inoue balloon technique¹ and the balloon size selection was made according to the Inoue criteria (Figure 2).¹ Stepwise echo/Doppler mitral balloon dilatation was done according to the Inoue technique. The total procedure time was taken as skin to skin. The mitral valve area was calculated using the Gorlin formula with direct left atrial/left ventricular transmitral pressure gradient. The Gorlin mitral valve area was measured before and after balloon valvotomy. Cardi-

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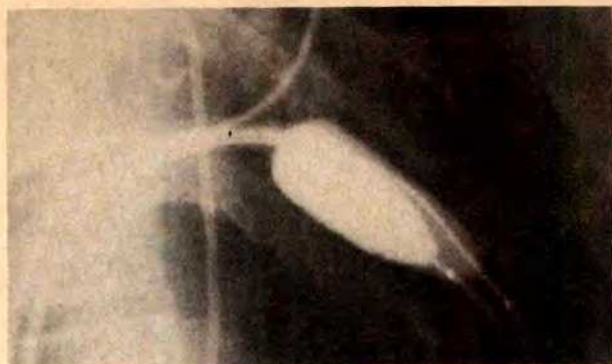


FIGURE 1. Double balloon valvotomy technique using the 2 Mansfield balloon catheters in a patient from group 1.

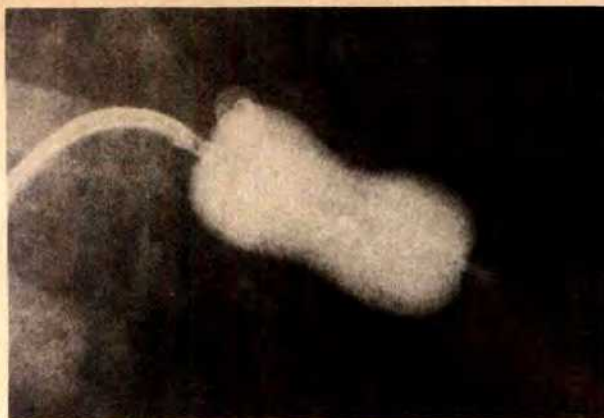


FIGURE 2. Inoue balloon valvotomy in a patient from group 2.

ac output was measured using the thermodilution technique. Left ventricular angiography was performed both before and after balloon valvotomy. The angiographic degree of mitral regurgitation was assessed using the Sellers classification.

Mean \pm standard deviation was calculated in the usual way. A Student's *t* test was used to test the significance between the means.

Group 1: The mean mitral valve area increased from 0.8 ± 0.2 to 1.9 ± 0.5 cm² ($p < 0.001$). One patient developed grade I mitral regurgitation. Residual stenosis persisted in 1 patient with a mitral valve area < 1.5 cm². The mean total procedure time was 220 ± 30 minutes.

Group 2: The mean mitral valve area increased from 0.8 ± 0.2 to 1.8 ± 0.5 cm² ($p < 0.01$). The degree of mitral regurgitation increased from grade I to II in 1 patient. Residual stenosis persisted in 2 patients with mitral valve area ≤ 1.5 cm². The mean total procedure time was 140 ± 41 minutes.

Mitral balloon valvotomy is an established therapeutic alternative to the surgical treatment of mitral stenosis.¹⁻⁴ The mechanism of both single and double mitral balloon valvotomy is similar to surgical valvotomy, i.e., commissural splitting.¹⁻⁵ This study has clearly shown that the mitral valve area achieved after balloon valvotomy is similar using both the Inoue and the double balloon Mansfield technique. Both groups of patients had comparable mitral valve and subvalvular anatomy as evaluated by echocardiography. Previous published series of the Inoue balloon and the double balloon mitral valvotomy techniques included a heterogeneous population of patients¹⁻⁴ with noncomparable mitral valve and subvalvular apparatus. Studies, both in vitro and in vivo, demonstrated that the mitral and subvalvular apparatus status were the major determining factors in achieving good mitral valve areas after balloon valvotomy.^{1-3,4,6}

Our study included 2 small groups of patients with similar valvular and subvalvular anatomy. Larger studies comparing these 2 techniques are required to evaluate the incidence of iatrogenic mitral regurgitation between the 2 different techniques. The incidence of iatrogenic atrial septal defects is small using either technique.¹⁻³

The double balloon technique using the long transeptal sheath is difficult to master. The Inoue balloon technique is less demanding than the double balloon technique and consequently decreases the total procedure time significantly. This advantage may be outweighed by the expense of the balloon catheter: 4 times that of 2 standard Mansfield balloon catheters. This factor is particularly relevant in third world countries where mitral valve stenosis is prevalent.

We conclude that both the Inoue balloon catheter and the double balloon technique achieve similar mitral valve areas. The Inoue balloon is technically less demanding and decreases total procedure time, compared with the double balloon Mansfield technique. This advantage should be weighed against the expense of the device.

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Transesophageal Echocardiographic Features of Stenotic Bioprosthetic Valves in the Mitral and Tricuspid Valve Positions

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A frequent long-term complication of bioprosthetic valves is spontaneous degeneration of the cusps with clinical features of valve regurgitation or, less frequently, valve stenosis.¹ Transthoracic echocardiography with cardiac Doppler is valuable in diagnosing stenosis of bioprosthetic valves.² However, a major drawback of this approach is that all 3 bioprosthetic cusps are not consistently demonstrated owing to sound attenuation from the intervening chest wall and lungs, and to reverberation from the metal portion of the valve ring and stents. These problems are usually overcome by using a transesophageal ultrasound probe. We recently described our transesophageal echocardiographic investigations in predominantly regurgitant bioprosthetic valves.³ Those patients are not included in this study. To the best of our knowledge, there are no reports on stenotic bioprostheses studied by transesophageal echocardiography.

Transesophageal (single-plane) and transthoracic echocardiography, and color flow Doppler studies were performed in 27 bioprosthetic mitral and tricuspid valves implanted in 24 patients using standard equipment (Hewlett-Packard Sonar 500 and 1000) and techniques.⁴ Nineteen patients with 21 bioprostheses (19 mitral and 2 tricuspid) were clinically normal without cardiac symptoms or regurgitation murmurs, whereas the remaining 5 patients with 5 mitral and 1 tricuspid prosthesis presented with symptoms of progressive dyspnea or congestive heart failure, or both. Diagnosis of valve stenosis was subsequently confirmed in these symptomatic patients by cardiac catheterization and angiography performed in 5 patients and by valve replacement surgery in 6. None of the patients at presentation had active infective endocarditis.

Ultrasound tests were performed on the same day in 20 patients and the valve cusps were identified from the stents by their opening and closing motions. If the cusps had a dense, bright appearance, they were deemed to be thick. The cusps were measured at their maximal thickness site during systole. The valve cusp separation at its narrowest point was measured in early diastole by frame-by-frame analysis on video-

tape. Transthoracic continuous-wave Doppler was used to obtain peak transmitral and tricuspid flow velocities. Mean valve gradient (Bernoulli equation) and valve area (pressure half-time method) were then calculated using an on-line computer. All valves were interrogated by color flow Doppler for the presence or absence of valve regurgitation and, once identified, it was semiquantitated by previously described techniques.⁵

Transthoracic echocardiography demonstrated limited segments of valve cusps in 15 cases, but failed to demonstrate any cusp in 6 other normal valves. Because all 3 cusps could not be visualized by this approach, the cusp separation could not be measured. Mean Doppler mitral valve gradient was 7 ± 4 mm Hg and mean valve area was 2.1 ± 0.7 cm². Mild mitral regurgitation was demonstrated by color flow Doppler in 2 cases.

Transesophageal imaging clearly demonstrated all valve cusps which had fine linear appearance (thin) in 17 cases (Figure 1), and dense, bright ap-

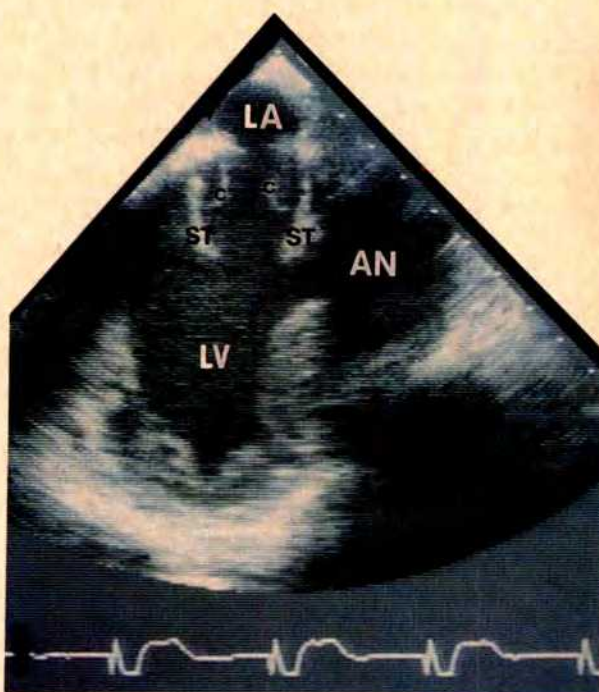


FIGURE 1. Transesophageal 2-dimensional echocardiogram of patient with normal functioning bioprosthetic mitral valve. Note thin cusp (c) in its open position. This patient, incidentally, also had submitral left ventricular aneurysm (AN). LA = left atrium; LV = left ventricle; ST = valve stents.

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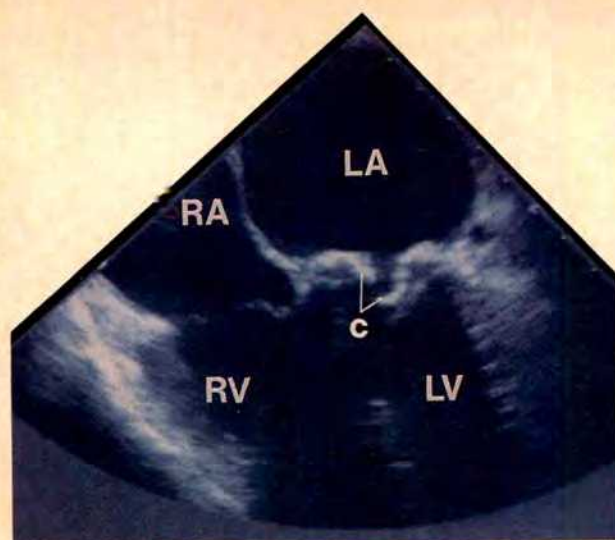


FIGURE 2. Transesophageal 2-dimensional echocardiogram of patient with stenotic bioprosthetic mitral valve. Note dense, bright cusp (c) echoes with restricted opening during diastole. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

pearance (thick) in 4. Thin valves had a maximal cusp thickness of 1.5 to 2 mm and thick nonstenotic valves 2 to 3 mm. Diastolic cusp separation varied in clinically normal valves from 1.0 to 1.8 cm (mean 1.4). Mild mitral regurgitation was demonstrated in 6 bioprostheses.

Transesophageal echocardiography failed to demonstrate the valve cusps in 3 of 6 stenotic valves. In 3 other cases, dense and bright cusp echoes were demonstrated, suggesting thick or calcified valves, or both. Mean Doppler mitral/tricuspid valve gradient was 14 ± 4 mm Hg and mean valve area 1.01 ± 0.3 cm² compared with 18 ± 4 mm Hg and 0.8 ± 0.2 cm², respectively, by cardiac catheterization. Mild mitral/tricuspid regurgitation was present in 2 patients by transthoracic color flow Doppler.

Transesophageal 2-dimensional echocardiography of the stenotic valves, however, clearly demonstrated all valve cusps with areas of thickening measuring 3 to 6 mm involving 1 or more cusps in all 6 cases (Figure 2). Furthermore, cusp mobility was severely restricted with cusp separation measuring 0.3 to 0.7 cm (mean 0.5). Color flow Doppler demonstrated concomitant mild mitral/tricuspid valve regurgitation in 4 patients (Figure 3) and moderate mitral regurgitation in 1.

Diagnosis of bioprosthetic mitral and tricuspid valve stenoses may be difficult. The cardiac auscultatory findings are not very specific because an opening sound and diastolic rumble can be heard in normal functioning mitral and tricuspid bioprostheses. Consequently, these pa-

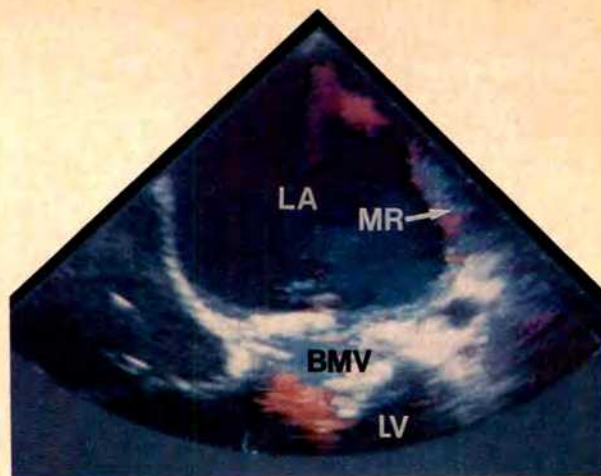


FIGURE 3. Transesophageal color flow Doppler of patient in Figure 2 with stenotic bioprosthetic mitral valve (BMV). Note narrow mitral regurgitant jet (MR) occupying <20% of left atrial chamber. LA = left atrium; LV = left ventricle.

tients are often undiagnosed until they develop decompensated congestive heart failure.

Transesophageal 2-dimensional echocardiography was excellent in demonstrating the presence or absence of thin or thick valve cusps with normal or restricted cusp opening. The features of thickened and calcified valve cusps were subsequently confirmed during surgery in all stenotic bioprostheses. In clinically normal functioning valves, the mere presence of a thick cusp by itself does not indicate severe stenosis and the need for valve replacement surgery. However, in the absence of endocarditis and thrombus formation, a thick valve may represent subclinical degeneration.² Patients with severe valve stenosis can be distinguished from these patients by cusp thickness >3 mm and cusp opening <0.7 cm with transesophageal 2-dimensional echocardiography, and by valve area <1.0 cm² with cardiac Doppler and catheterization. In conclusion, transesophageal echocardiography complements transthoracic imaging in diagnosing bioprosthetic mitral and tricuspid valve stenoses.

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Diagnosis of Patent Ductus Arteriosus in Adults by Biplane Transesophageal Color Doppler Flow Mapping

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In infants and children, direct visualization of patent ductus arteriosus and shunt flow is often successful using transthoracic 2-dimensional¹ and color Doppler echocardiography.² In adults, however, transthoracic echocardiography may fail to yield diagnostic information on patent ductus arteriosus because the ductus is located far from the transducer on the chest wall.³ Since the recent development of a transesophageal transducer with the capabilities of color-coded Doppler flow imaging, both single- and biplane transesophageal echocardiography have been extensively used in the assessment of patients with cardiovascular diseases.⁴⁻⁸ Transesophageal approach affords consistent high-quality 2-dimensional images of the arch and descending aorta without being restricted by lung tissue or ribs. This study evaluates the diagnostic usefulness of transthoracic and biplane transesophageal color Doppler echocardiography in adolescent and adult patients with patent ductus arteriosus.

The study group consisted of 8 patients (2 men and 6 women, mean age \pm standard deviation 40 ± 18 years, range 16 to 62) with patent ductus arteriosus diagnosed by cardiac catheterization. In 5 patients, diagnosis was confirmed surgically. Phonocardiography revealed continuous murmur in all 8 patients.

The ultrasound systems used in this study were the Toshiba SSH-160A with a transducer of 2.5 MHz and 96 elements for transthoracic examination, and the Aloka SSD-870 with a biplane transesophageal probe for transesophageal examination. The biplane transesophageal probe is equipped with 2 transducers of 5.0 MHz and 32 elements, 1 for transverse scan and the other for longitudinal scan.

All patients were examined by transthoracic echocardiography in the left lateral position from a standard parasternal short-axis view at the level of the great arteries. Shunt flow from the aorta into the pulmonary artery was searched carefully.

After pharyngeal anesthesia with aerosol and viscous lidocaine, the transesophageal probe was introduced into the esophagus with the patient in the left lateral position. The descending aorta was visualized as a pulsating circular structure with a transverse

scan transducer at a distance of 30 cm from the patient's teeth, and the probe was pulled out carefully in search of ductal shunt flow from the aorta into the pulmonary artery. Subsequently, a longitudinal scan transducer was used to search for ductal shunt flow.

With transthoracic color flow mapping, left-to-right shunt flow was visualized from the distal to proximal pulmonary trunk in 4 patients (Table I) and from the mid- to proximal pulmonary trunk in 2 (Figure 1). In the remaining 2 patients, abnormal flow could not be detected in the pulmonary trunk. Flow in the ductus itself or the aorta was not clearly visualized in any patients by transthoracic approach. Using biplane transesophageal color flow mapping, left to right shunt flow from the aorta through the ductus into the pulmonary artery was visualized on the same cross-section in 5 patients with a transverse scan transducer, and in all 8 with a longitudinal scan transducer (Table I).

Detection of turbulent flow in the pulmonary artery with pulsed or color Doppler echocardiography is not enough to diagnose patent ductus arteriosus. Turbulent flow can occur in several cardiovascular disorders such as aortopulmonary septal defect, rupture of aortic aneurysm into pulmonary artery, pulmonary stenosis, constriction of main pulmonary artery, and coronary artery fistula draining into the pulmonary trunk.⁹ To rule out these conditions, shunt flow in the pulmonary trunk must be shown to originate from the ductus. Based on the results of this study, transthoracic color flow mapping does not seem to be always useful in establishing diagnosis of patent ductus arteriosus in adolescent and adult

TABLE I Echocardiographic Results

Pt. No.	Age (yr) & Sex	TTE	TEE (T)	TEE (L)
1	16 F	+	+	+
2	25 F	+	+	+
3	43 F	+	+	+
4	54 F	+	0	+
5	62 M	0	+	+
6	19 M	0	+	+
7	40 F	0	0	+
8	57 F	0	0	+

For transthoracic echocardiography (TTE), + and 0 indicate presence and absence of left-to-right shunt flow distal to proximal pulmonary trunk. For transesophageal echocardiography (TEE), + and 0 indicate presence and absence of left-to-right shunt flow from the descending aorta through the ductus into the pulmonary artery visualized on the same cross section. L = longitudinal scan; T = transverse scan.

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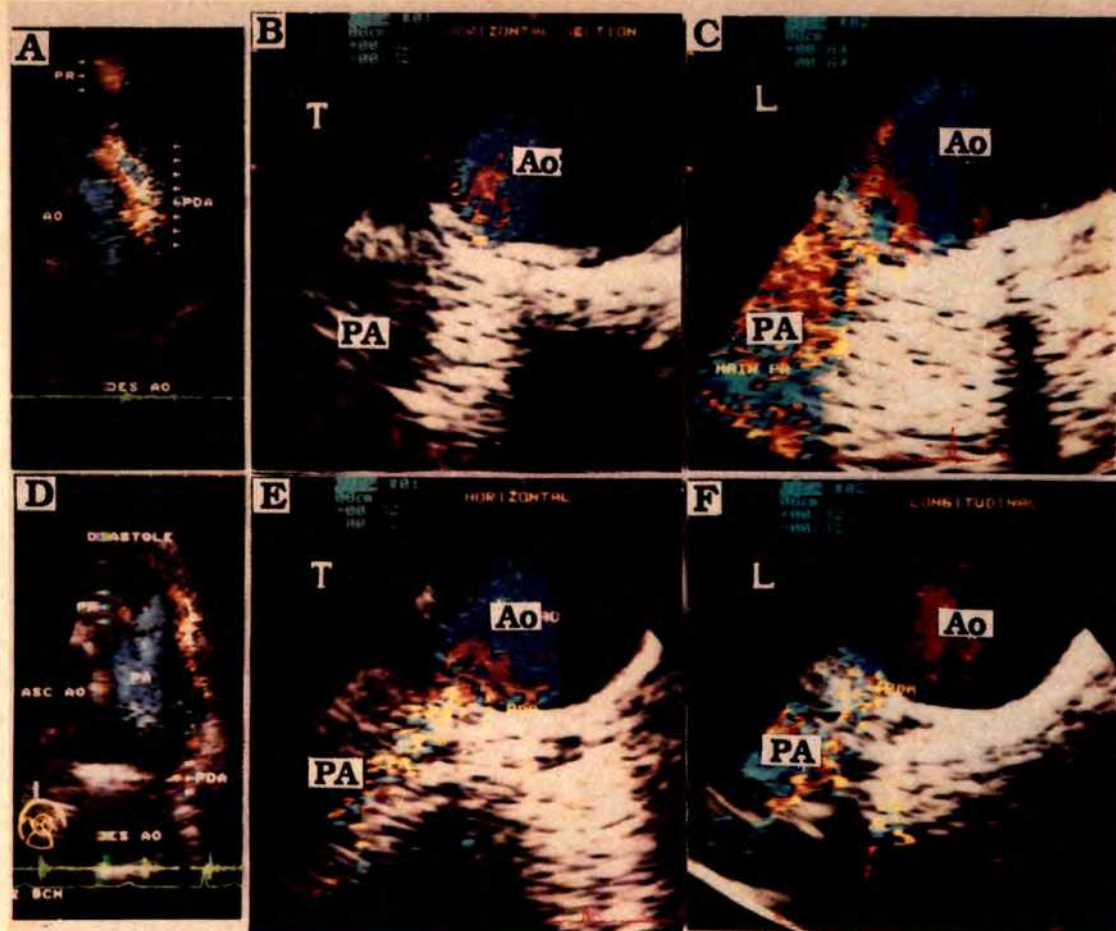


FIGURE 1. Transthoracic (A and D) and transesophageal (transverse [B and E] and longitudinal [C and F] scans) echocardiograms from 2 patients with patent ductus arteriosus (PDA). In patient 7 (A to C), shunt flow could not be visualized in the distal pulmonary trunk with transthoracic echocardiography (A), and shunt flow was visualized from the aorta (AO) through the ductus into the pulmonary artery (PA) on the same cross section only with transesophageal longitudinal scan (C). In patient 1 (D to F), shunt flow was visualized from the distal to the proximal pulmonary trunk with transthoracic echocardiography (D), and shunt flow was visualized from the aorta through the ductus into the pulmonary artery on the same cross section with both transesophageal transverse (E) and longitudinal (F) scans. ASC = ascending; DES = descending; L = longitudinal scan; T = transverse scan.

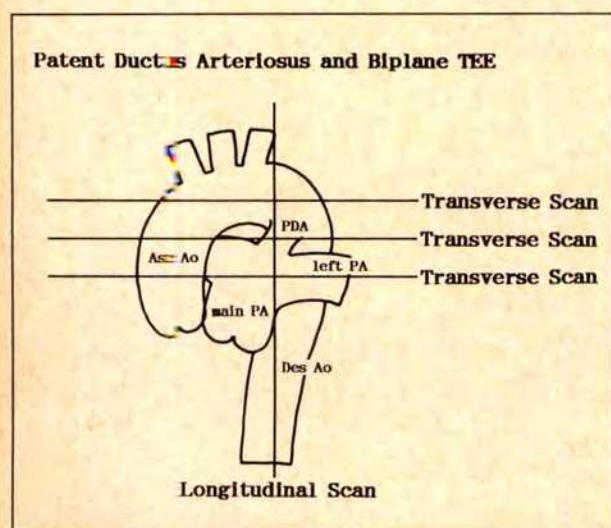


FIGURE 2. Schematic drawing showing transverse and longitudinal sections of biplane transesophageal echocardiography in patients with patent ductus arteriosus (PDA). AO = aorta; PA = pulmonary artery.

patients. In contrast, color flow mapping using a transesophageal biplane probe equipped with 2 transducers for transverse and longitudinal scan is the most useful noninvasive means of visualizing shunt flow in the ductus itself and the surrounding structure in adolescent and adult patients with patent ductus arteriosus. Biplane transesophageal probe was developed to overcome the disadvantage of single-plane probe that the transducer in the esophagus is less movable than the conventional transducer on the chest wall.⁵⁻⁸ In this report, longitudinal scan seems more useful than transverse scan in displaying shunt flow from the aorta to the pulmonary artery on the same cross-section. This might be explained by the fact that the aorta, ductus and pulmonary artery frequently lie parallel to the esophagus (Figure 2).

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Echo-Doppler Study of Right Ventricular Filling in Asymptomatic Patients with Senning Operation for Transposition of the Great Arteries

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The noninvasive evaluation of left ventricular diastolic function using pulsed Doppler echocardiography has gained widespread attention with the validation of several indexes with regard to contrast angiography,¹ radionuclide angiography² and hemodynamic parameters.³ However, limited data have been reported concerning the use of Doppler echocardiography to assess the inflow characteristics of the systemic right ventricle. The purpose of this study was to perform a noninvasive evaluation of right ventricular filling characteristics in a selected group of asymptomatic patients who underwent the Senning operation for simple transposition of the great arteries, using pulsed Doppler echocardiography.

A selected group of 27 patients (17 male and 10 female, aged 1.6 to 10.5 years, mean \pm standard deviation 6 ± 2) were studied 0.6 to 9.8 years (mean 4.9 ± 2.3) after having undergone the Senning operation for simple transposition of the great arteries. All patients were asymptomatic, had no significant residual defects on physical examination, electrocardiogram and chest x-ray and were taking no medication. The patients were classified into 2 groups on the basis of the degree of tricuspid regurgitation diagnosed by echo-Doppler: group I ($n = 17$) without or with only trivial regurgitation, and group II ($n = 10$) with moderate or moderately severe regurgitation. The measurements from tricuspid ($n = 10$) and mitral ($n = 10$) pulsed Doppler flow recordings from normal age-matched children were used for comparison.

A complete echocardiographic study was performed using an Aloka SSD 860 equipped with 5- and 3.5-MHz transducers, to exclude obstruction to the pulmonary or systemic venous return, baffle leak, significant pulmonary stenosis or hypertension. Global right ventricular systolic function was evaluated using aortic continuous-wave Doppler recordings as described⁴: preejection time (PET), ejection time (ET), acceleration time and peak velocity. From these measurements the PET/ET ratio, acceleration to ET ratio and mean aortic acceleration were calculated. Using the apical 4-chamber view and guided by color flow Doppler, the Doppler sample volume was placed at

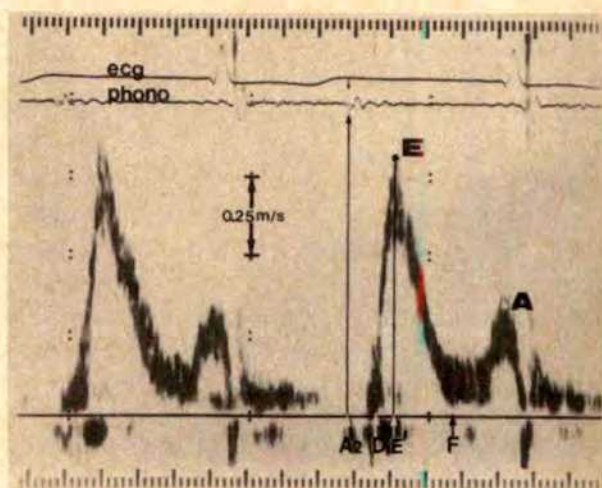


FIGURE 1. Pulsed Doppler tricuspid flow velocity signal with simultaneous electrocardiogram (ecg) and phonocardiogram (phono) from an asymptomatic patient having undergone the Senning operation for transposition of the great arteries. The variables of diastolic function measured include: peak early (E) and atrial (A) flow velocities, isovolumic relaxation time (A2-D), acceleration (D-E') and deceleration (E'-F) time of E, and percent atrial contribution to filling.

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TABLE I Echo-Doppler Indexes of Right Ventricular Systolic Function in Patients Without (group I) and With (group II) Tricuspid Regurgitation

	Group I (n = 17)	Group II (n = 10)	p Value
Heart rate (beats/min)	85 ± 11	87 ± 7	NS
Preejection time (ms)	104 ± 10	95 ± 11	0.02
Ejection time (ms)	263 ± 23	262 ± 8	NS
Preejection time/ejection time	0.40 ± 0.04	0.36 ± 0.04	0.03
Acceleration time (ms)	85 ± 7	84 ± 5	NS
Acceleration time/ejection time	0.33 ± 0.04	0.32 ± 0.03	NS
Peak aortic flow velocity (cm/s)	102 ± 5	106 ± 12	NS
Mean aortic flow acceleration (m/s ²)	12.0 ± 0.8	12.6 ± 1.5	NS

Values are mean ± standard deviation.
NS = not significant.

TABLE II Pulsed Doppler Measurements in Group I Patients and Normal Children

	Group I (n = 17)	Normal Subjects	
		RV Filling (n = 10)	LV Filling (n = 10)
Heart rate (beats/min)	81 ± 10	78 ± 7	83 ± 12
Early peak flow velocity (cm/s)	96 ± 16*†	74 ± 15	113 ± 7
Atrial peak flow velocity (cm/s)	55 ± 12*	44 ± 9	57 ± 11
Early/atrial velocity	1.81 ± 0.42†	1.75 ± 0.23	2.10 ± 0.40
Acceleration time (ms)	63 ± 10*	75 ± 14	64 ± 10
Deceleration time (ms)	115 ± 28	120 ± 22	109 ± 15
Atrial contribution to filling	0.23 ± 0.03	0.21 ± 0.02	0.24 ± 0.03
Isovolumic relaxation time (ms)	64 ± 6*†	30 ± 15	46 ± 8

*p < 0.05 vs normal right ventricular filling; †p < 0.05 vs normal left ventricular filling.
Values are mean ± standard deviation.
LV = left ventricular; RV = right ventricular.

the tips of the tricuspid leaflets, where the highest velocities with least spectral dispersion were obtained. Tricuspid flow velocity signals were recorded simultaneously with an electrocardiographic lead and phonocardiogram at a paper speed of 50 or 100 mm/s. The following variables of right ventricular diastolic function were measured (Figure 1): peak early, peak atrial and early to atrial flow velocity ratio; isovolumic relaxation time (time from aortic closure on the phono to the onset of tricuspid flow); acceleration and deceleration time of early peak flow, and percent atrial contribution to filling (atrial velocity-time integral/total velocity-time integral). All measurements were calculated as a mean of 3 to 5 consecutive cardiac cycles recorded during quiet respiration. Extra- and postextrasystolic beats were excluded. The data were compared using an unpaired t test and a p value < 0.05 was considered significant. The beat-to-beat variation coefficients for selected diastolic measurements were calculated from 3 consecutive cardiac cycles of 8 patients from group I: peak early (6%) and peak atrial (5%) flow velocity; acceleration (5%) and decelera-

TABLE III Tricuspid Regurgitation Influence on Right Ventricular Filling in Asymptomatic Patients

	Group I (n = 17)	Group II (n = 10)	p Value
Heart rate (beats/min)	81 ± 10	84 ± 6	NS
Early peak flow velocity (cm/s)	96 ± 16	122 ± 23	0.001
Atrial peak flow velocity (cm/s)	55 ± 12	48 ± 13	NS
Early/atrial velocity	1.81 ± 0.42	2.61 ± 0.33	< 0.001
Acceleration time (ms)	63 ± 10	55 ± 7	0.04
Deceleration time (ms)	115 ± 28	133 ± 21	NS
Atrial contribution to filling	0.23 ± 0.03	0.20 ± 0.03	NS
Isovolumic relaxation time (ms)	64 ± 6	67 ± 9	NS

Values are mean ± standard deviation.
NS = not significant.

tion (7%) time of early flow; isovolumic relaxation time (7%) and percent atrial contribution to filling (6%).

The echo-Doppler indexes of right ventricular systolic function from patients with Senning operation are presented in Table I. Patients in group II had a significantly shorter PET ($p = 0.02$) and PET/ET ($p = 0.03$) than group I patients. None of the other studied parameters was significantly different between the 2 groups. Pulsed Doppler diastolic time intervals and velocity data in group I patients and normal subjects are summarized in Table II. Group I patients had significantly greater peak early ($p = 0.001$) and peak atrial ($p = 0.02$) flow velocities, isovolumic relaxation time ($p < 0.001$) and shorter acceleration time of early peak flow ($p = 0.02$) than normal tricuspid flow. Compared with normal mitral flow, group I patients also had significantly greater isovolumic relaxation time ($p < 0.001$), shorter early peak flow velocity ($p = 0.001$) and early to atrial ratio ($p < 0.001$). None of the remaining parameters was significantly different. The influence of tricuspid regurgitation on right ventricular filling is shown in Table III. Group II patients had a significantly greater peak early ($p = 0.001$), early to atrial ratio ($p < 0.001$) and a shorter acceleration time of early peak flow ($p = 0.04$) than group I patients. The remaining studied parameters were not significantly influenced by tricuspid regurgitation.

After the Senning operation there is concern about the capacity of the right ventricle to support systemic pressure. Evaluation of this issue requires longitudinal studies, and echocardiography seems the best method for serial comparisons. M-mode,⁵ 2-dimensional echocardiography⁶ and echo-Doppler⁴ has been used to evaluate right ventricular systolic function but not to identify diastolic filling properties. Our study shows that right ventricular filling characteristics in asymptomatic patients who underwent the Senning operation for simple transposition of the great arteries, detectable by tricuspid flow Doppler recording, are markedly different from normal, having a mitral-like flow pattern.

The mechanism for this right ventricular filling pattern has not been clearly studied. The intraatrial baffle used in physiologic surgical repair of transposition of the great arteries limits the invasive and noninvasive study of right ventricular diastolic function. Catheterization of the neopulmonary venous atrium may be difficult in the absence of a baffle leak and requires arterial catheterization. Furthermore, the alternative represented by the echo-Doppler is confronted with the absence of a specific control group because the right ventricle receives pulmonary venous blood from a surgically elongated atrium. The right ventricular filling pattern that we documented could be a result of abnormal ventricular relaxation and decreased operative compliance due to an increased modulus of chamber stiffness. Because we did not obtain simultaneous invasive hemodynamic data, we could not establish which factors were the most important. However, studies of left ventricular diastolic Doppler flow profiles³ indicate that, in our patients, reduction in right ventricular chamber compliance with elevated filling pressure and the larger size of the tricuspid valve orifice seem to be the dominant factors that partially overwhelm the effect of a reduced rate of ventricular relaxation. The consequence of high systolic and low systolic pressures in the right and left ventricles, respectively, is an abnormal ventricular geometry with a dilated and hypertrophied right ventricle.⁷ This abnormal ventricular geometry with an increased right ventricular mass is certainly responsible for an increased ventricular stiffness.⁷ Preoperative hypoxia and permanent systolic pressure overload can cause abnormal intrinsic muscular stiffness. Other potential factors influencing the right ventricular filling pattern include the postoperative adhesion of the free

wall to the anterior chest wall, age at surgery, respiration, and the angle between the Doppler beam and blood flow direction.

Our study shows that asymptomatic patients undergoing a Senning procedure for simple transposition of the great arteries have a peculiar right ventricular filling pattern. The data suggest significant abnormalities on right ventricular relaxation and operative compliance. The presence of tricuspid regurgitation can influence some of the right ventricular filling parameters, even when the patient maintains a satisfying systolic function. Furthermore, Doppler indexes of diastolic function provide a noninvasive alternative for the serial assessment of right ventricular function in this group of patients.

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Incidence and Significance of a "Step-Down" in Oxygen Saturation from Superior Vena Cava to Pulmonary Artery

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Several studies¹⁻⁴ have assessed the normal variability of oxygen saturations in blood from the right-sided heart chambers. An increase in saturation from the peripheral to the central chambers that exceeds this variability suggests left-to-right intracardiac shunting. In some subjects, a decrease in saturation from the superior vena cava (SVC) to the central right-sided chambers occurs. In previous studies,^{5,6} such a "step-

down" was often observed in patients with shock. This study was performed to assess the incidence of a step-down in oxygen saturation of $\geq 5\%$ from the SVC to the pulmonary artery (PA) and to determine if such a step-down is associated with cardiac or renal dysfunction.

We reviewed all combined right- and left-sided cardiac catheterizations performed at Parkland Memorial Hospital, Dallas, Texas, from 1978 to 1990. Of 3,296 patients, the oxygen saturation of blood from the SVC exceeded that from the PA by $\geq 5\%$ in 177 (5.4%) (57 men, 120 women, age range 18 to 88 years). Each subject was matched with the next patient having combined right- and left-sided cardiac catheterization who had neither a $\geq 5\%$ SVC-PA step-

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TABLE I Comparison of Patients With and Without a $\geq 5\%$ SVC-PA Step-Down in Oxygen Saturation			
	Step-Down Present (n = 177)	Control Subjects (n = 177)	p Value
Age (years)	53 \pm 14	51 \pm 14	NS
Cardiac output (L/min/m ²)	2.7 \pm 0.8	2.6 \pm 0.7	NS
Mean PA wedge pressure (mm Hg)	19 \pm 10	13 \pm 8	<0.001
Mean PA pressure (mm Hg)	30 \pm 13	22 \pm 10	<0.001
Mean RA pressure (mm Hg)	8 \pm 6	6 \pm 4	<0.001
Left ventricular ejection fraction	0.52 \pm 0.19	0.54 \pm 0.16	NS
Serum creatinine (mg/dl)	2.0 \pm 2.7	1.2 \pm 0.4	<0.001
All data are mean \pm 1 standard deviation. NS = not significant; PA = pulmonary artery; RA = right atrial; SVC = superior vena cava.			

TABLE II Incidence of Abnormal Hemodynamic and Angiographic Variables in Subjects With and Without a $\geq 5\%$ SVC-PA Step-Down in Oxygen Saturation			
	Step-Down Present (n = 177)	Control Subjects (n = 177)	p Value
Cardiac output < 2.2 L/min/m ²	47/175 (27%)	45/175 (26%)	NS
Mean PA wedge pressure > 18 mm Hg	88/176 (50%)	37/174 (21%)	<0.001
Mean PA pressure > 30 mm Hg	76/176 (43%)	31/176 (18%)	<0.001
Mean RA pressure > 8 mm Hg	62/175 (35%)	33/175 (19%)	0.01
Left ventricular ejection fraction < 0.40	36/157 (23%)	30/166 (18%)	NS
All data are mean \pm 1 standard deviation. Abbreviations as in Table I.			

down nor evidence of left-to-right intracardiac shunting. This control group contained 97 men and 80 women (age range 15 to 79 years).

In each patient, a catheter was advanced sequentially to the SVC, the right atrium and the main PA. Single, 2-ml blood samples were obtained within 5 minutes from the SVC and the PA, and their oxygen saturations were determined with a reflectance oximeter (American Optical) known to be accurate when saturation is 45 to 98%.⁷ Within 15 minutes, cardiac output was determined by the Fick principle; pulmonary capillary wedge, PA and right atrial pressures were recorded, and left ventriculography was performed, from which ejection fraction was calculated. Finally, serum creatinine at the time of catheterization was recorded.

All data are reported as mean \pm 1 standard deviation. For each variable, patients with an SVC-PA step-down $\geq 5\%$ were compared with control subjects

using Student's *t* test. The frequency with which each variable was abnormal in the 2 groups was compared using a chi-square analysis. A *p* value <0.05 was considered significant.

For the 177 patients with an SVC-PA step-down, catheterization revealed no disease in 10, coronary artery disease in 71, valve disease in 52, cardiomyopathy in 30, pericardial disease in 7, pulmonary hypertension in 4 and high-output failure in 3. For these subjects, SVC saturation was 69 \pm 10% and PA saturation was 62 \pm 11% (*p* <0.001 in comparison with SVC). For the 177 control subjects, catheterization revealed no disease in 18, coronary artery disease in 98, valve disease in 37, cardiomyopathy in 21, pericardial disease in 2 and pulmonary hypertension in 1. For these subjects, SVC saturation was 68 \pm 8% and PA saturation was 68 \pm 9% (*p* = not significant in comparison with SVC). Patients with an SVC-PA step-down were similar to the control subjects in age, cardiac output and ejection fraction. Mean pulmonary capillary wedge, PA and right atrial pressures were higher (*p* <0.001) in subjects with a step-down, as was serum creatinine concentration (Table I). The incidence of reduced cardiac output or ejection fraction was similar in the 2 groups, but subjects with a step-down were more likely to have a mean wedge pressure >18 mm Hg, a mean PA pressure >30 mm Hg and a mean right atrial pressure >8 mm Hg (Table II).

In control subjects, oxygen saturation of inferior vena caval blood is often high because of the contribution of renal venous effluent that is highly saturated.⁸ Thus, blood from the PA is usually more saturated with oxygen than that from the SVC.¹ In patients with shock, heart failure or renal disease, renal blood flow may decrease^{9,10} so that renal venous effluent contributes less to the saturation of inferior vena caval blood. Because cerebral blood flow is preserved,¹¹ the saturation of blood obtained from the SVC may be higher than that from the inferior vena cava and the PA. In patients with shock of various causes, oxygen saturation of blood from the SVC was consistently higher than that from the PA.^{5,6}

In this study, we found that the saturation of blood from the SVC exceeded that from the PA by $\geq 5\%$ in only 177 of 3,296 patients (5.4%). We tried to determine if a step-down in oxygen saturation was associated with: (1) cardiac or renal dysfunction, or both, as reflected by inadequate peripheral perfusion (manifested by low cardiac output); (2) diminished left ventricular performance (manifested by a depressed ejection fraction); (3) pulmonary vascular congestion (manifested by a high wedge pressure), with a resultant increase in PA and right atrial pressures; and/or (4) reduced renal function (manifested by an elevated serum creatinine concentration). In patients with these derangements, the saturation of inferior vena caval blood may be lower than that of SVC blood,

at least in part because of reduced renal blood flow. As a result, these patients may have an oxygen saturation in PA blood lower than that of SVC blood. In our 177 subjects with an SVC-PA step-down, cardiac output and ejection fraction were similar to those of the control subjects (Table I), and the 2 groups had a similar incidence of abnormal values for these variables (Table II). However, patients with an SVC-PA step-down had higher pulmonary capillary wedge, PA and right atrial pressures than the control subjects (Table I), and the incidence with which these pressures were elevated was greater in those with a step-down (Table II). In addition, serum creatinine was higher in patients with a step-down than in control subjects. Although renal blood flow is often reduced in patients with renal disease of various etiologies, renal oxygen extraction is usually not altered. Thus, it is possible that the renal contribution to inferior vena caval blood flow is diminished in subjects with an SVC-PA step-down. Because we did not measure renal blood flow, we are uncertain if this hypothesis is correct.

In conclusion, a decrease in oxygen saturation of $\geq 5\%$ from the SVC to the PA occurs infrequently. Subjects with such a step-down often have elevated pulmonary capillary wedge, PA and right atrial pressures, as well as elevated serum creatinine concentration. The mechanisms responsible for these observations are undefined, but it is possible that reduced renal blood flow (in

association with renal disease or decreased renal perfusion, or both) is at least partially responsible for our findings.

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Mitral and Pulmonary Venous Flow Under Influence of Positive End-Expiratory Pressure Ventilation Analyzed by Transesophageal Pulsed Doppler Echocardiography

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It has been known since 1948¹ that positive end-expiratory pressure (PEEP) ventilation causes a decrease in cardiac output. Since then, the effects of PEEP on the heart have been studied in detail. There are mainly 2 mechanisms discussed for the decrease in cardiac output with PEEP. The first hypothesis is that cardiac output is diminished by reduction of systemic venous return. This concept^{1,2} was questioned later by investigators^{3,4} who studied transmural pressures and found increased filling pressures with PEEP. They concluded that left ventricular compliance decreases with PEEP owing to interventricular septal shift from right ventricular overload⁴ or to compression of the heart by the expanded lungs. Subsequently, more precise measurements of filling pressure⁵ provided no evidence of decreased diastolic

compliance. Left ventricular function impairment could not be detected using either equilibrium-gated blood pool scintigraphy or transesophageal 2-dimensional echocardiography.⁶ Most examinations have relied on hemodynamic measurements that are dependent on intricate pressure recordings that are not always reliable.^{4,5} This study attempts to gain insight into changes in hemodynamics after induction of PEEP by measuring flow patterns with Doppler echocardiography. To examine the mechanism of reduction in cardiac output produced by high levels of PEEP ventilation, left atrial and left ventricular filling patterns were recorded with pulsed Doppler for 0- and 15-cm H₂O PEEP.

Fifteen patients (10 men and 5 women, mean age 58 years, range 29 to 75) were investigated. All 15 patients were undergoing prolonged mechanical ventilation for respiratory failure and were in sinus rhythm; patients undergoing mechanical ventilation for cardiac failure were excluded. Transesophageal

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pulsed Doppler echocardiography was used for recording flow velocities in the left upper pulmonary vein and the mitral valve. A Hewlett-Packard Sonos 500 with a 5-MHz transesophageal transducer was used for investigation. Mitral flow was sampled at the leaflet tips and pulmonary venous flow at least 1 cm upstream from the orifice of the left upper pulmonary vein. Flow velocities were recorded for 0- and 15-cm H₂O PEEP at expiration. The following measurements were obtained: For mitral valve flow, velocity-time integrals of E and A waves, total velocity-time integral and E/A ratio were calculated. For pulmonary venous flow, velocity-time integrals of systolic, diastolic and reverse flows, and total velocity-time integral were determined (Figure 1). Subsequently,

the systolic/diastolic flow ratio was calculated. From each recording, 3 consecutive beats were chosen for analysis and averaged. Differences were analyzed statistically by paired t test with a significance level of $p < 0.05$.

The change of heart rate (94 ± 22 to 92 ± 19 minutes⁻¹) with induction of PEEP was not significant. Mean blood pressure decreased significantly (90 ± 18 to 81 ± 19 mm Hg, $p < 0.01$) after induction of PEEP.

Induction of 15-cm H₂O PEEP resulted in a significant reduction of the total mitral valve velocity-time integral (15.2 to 12.0 cm, -21% , $p < 0.05$). The reduction of the velocity-time integral of the E wave (7.7 ± 3.0 to 5.3 ± 2.6 cm, -31% , $p < 0.01$) was larger

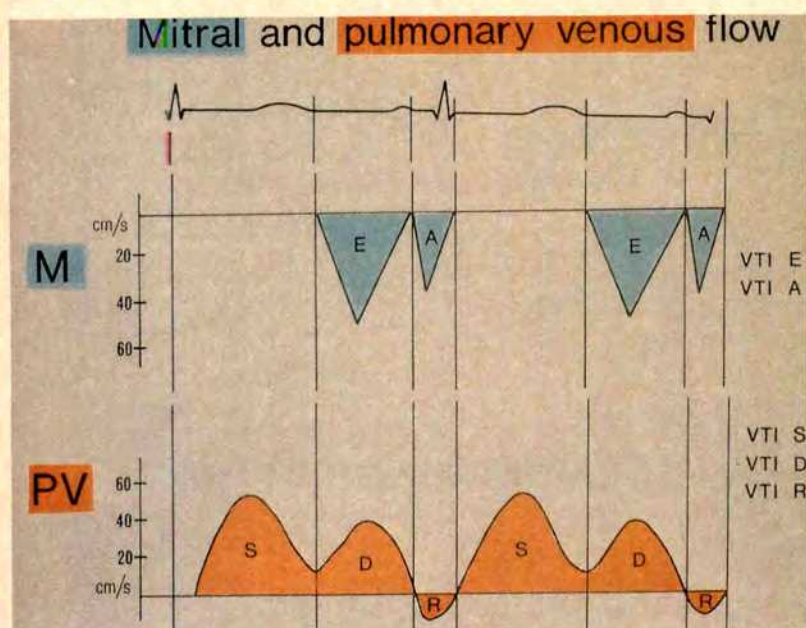


FIGURE 1. Mitral (M) and pulmonary venous (PV) flows are shown schematically. Velocity-time integrals (VTIs) of the E and A waves for mitral flow were measured. Velocity-time integrals of systolic (S), diastolic (D) and reverse (R) flows for pulmonary venous flow were determined.

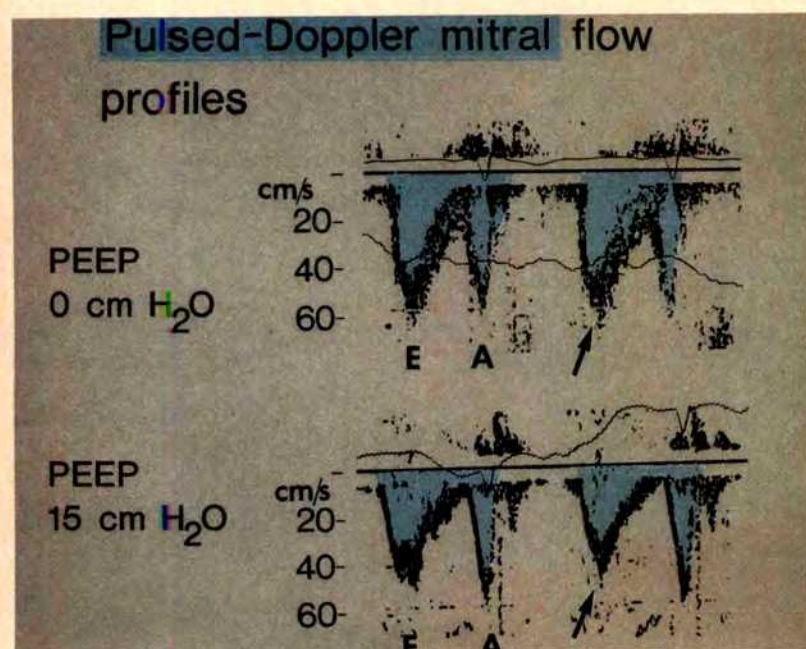


FIGURE 2. The pulsed Doppler mitral flow profile is shown for 0- and 15-cm H₂O positive end-expiratory pressure (PEEP). Arrow indicates that there is mainly a reduction of the E wave with induction of PEEP.

TABLE I Mitral and Pulmonary Venous Flow Variables With and Without PEEP

Pt. No.	M ₁₅		M ₀		PV ₁₅			PV ₀		
	E	A	E	A	S	D	R	S	D	R
1	2.5	14.0	3.4	14.4	2.3	1.3	0.6	2.3	1.4	0.6
2	2.8	9.5	4.8	8.5	4.3	1.8	0.8	5.9	3.0	0.7
3	7.7	7.1	10.3	8.7	10.3	4.1	1.2	12.8	5.6	1.7
4	4.7	10.3	11.6	15.0	7.3	2.1	1.3	8.0	4.0	1.3
5	8.1	3.9	9.5	4.2	10.2	6.9	0.5	10.0	8.9	1.1
6	3.5	3.9	5.2	4.2	16.9	6.2	1.0	21.4	14.1	1.3
7	2.8	1.9	3.9	2.1	9.8	8.9	0.9	9.5	14.4	1.4
8	4.0	1.9	10.0	7.4	6.3	4.1	0.8	16.3	7.4	0.5
9	6.9	6.4	8.9	8.9	4.5	2.5	0.6	7.9	4.7	0.6
10	4.2	4.3	5.2	5.0	11.6	11.1	1.1	14.4	8.1	1.4
11	7.9	8.6	11.0	10.4	15.0	1.9	1.2	17.2	2.6	1.5
12	10.6	4.4	10.9	4.8	9.0	7.5	1.0	8.8	8.3	1.0
13	4.5	4.8	5.4	3.9	5.5	3.2	1.1	8.0	8.5	2.0
14	6.9	9.6	9.7	10.5	11.7	7.5	0.8	14.8	10.4	0.7
15	3.2	3.0	6.0	3.9	5.7	1.9	1.0	7.2	3.7	1.2
\bar{X}	5.3	6.7	7.7	7.5	8.7	4.7	0.9	11.0	7.0	1.1
SD	± 2.6	± 3.5	± 3.0	± 4.1	± 4.2	± 3.1	± 0.2	± 5.2	± 4.0	± 0.5

E, A, S, D, R = velocity-time integrals in cm of the E, A, systolic, diastolic and reverse waves; M₁₅, M₀ = mitral flow variables with 15- or 0-mm Hg PEEP; PEEP = positive end-expiratory pressure; PV₁₅, PV₀ = pulmonary venous flow variables with 15- or 0-mm Hg PEEP; SD = standard deviation.

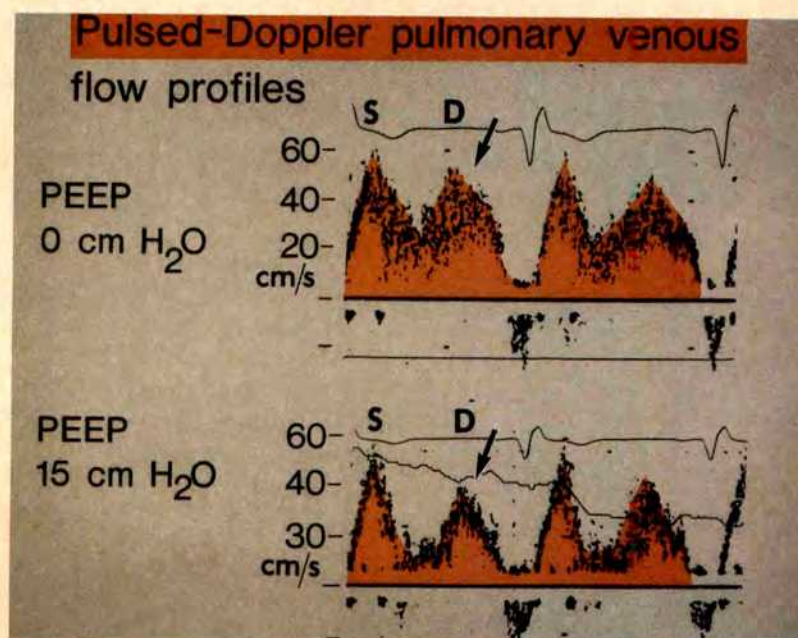
than that of the A wave (7.5 ± 4.1 to 6.7 ± 3.5 cm, -11% , p = not significant). As a result, the ratio of the velocity-time integral of the E to A waves decreased (1.3 to 1.0 , $p < 0.05$). Figure 2 shows an example of the patterns of expiratory mitral flow at PEEPs of 0- and 15-cm H₂O.

The total velocity-time integral of pulmonary venous flow declined by 25% (16.9 to 12.5 cm, $p < 0.05$) after induction of 15-cm H₂O PEEP compared with the basal condition. The reduction of systolic antegrade flow (11.0 ± 5.2 to 8.7 ± 4.2 cm, -21% , $p < 0.05$) was less than that of diastolic antegrade flow (7.0 ± 4.0 to 4.7 ± 3.1 cm, -32% , $p < 0.01$). As a result, the ratio of the velocity-time integral of systol-

ic to diastolic waves changed significantly (2.0 to 2.4 , $p < 0.05$). For diastolic retrograde reverse flow, there was a nonsignificant reduction of 18% (1.1 ± 0.5 to 0.9 ± 0.2 cm). The changes occurring in pulmonary venous flow with increase of PEEP (0- to 15-cm H₂O) are shown in Figure 3. Mitral and pulmonary venous flow variables with and without PEEP are listed for all 15 patients in Table I.

This study demonstrates a significant decrease in total mitral and pulmonary venous flow velocities with the administration of 15-cm H₂O of PEEP. This finding is not surprising, since decrease in cardiac output was first described in 1948.¹ The mitral flow pattern underwent a significant change of the E/A ratio (1.0 to 1.3) owing to

FIGURE 3. The pulsed Doppler pulmonary venous flow profile is shown for 0- and 15-cm H₂O positive end-expiratory pressure (PEEP). Arrow indicates that there is mainly a reduction of the diastolic (D) wave with induction of PEEP. S = systolic.



a larger decrease of the E wave with PEEP. Changes in mitral flow pattern with prominent A wave have been ascribed to reduced diastolic function.⁷ However, the E/A ratio has been found to be very dependent on left ventricular filling pressure.⁸ The E/A ratio can be reduced by altering the left ventricular preload. Our finding of a change in the E/A ratio in favor of the A wave might therefore result from either impaired left ventricular filling or reduced preload. To distinguish these conditions, we additionally investigated pulmonary venous flow. Previous studies have shown that pulmonary venous flow is influenced by dynamic changes in left atrial pressure and not by transmission of pressure pulse from the right ventricle.^{9,10} Therefore, pulmonary venous flow depends on the pressure gradient between the pulmonary veins and left atrium. The pulmonary venous systolic wave results from a decrease in left atrial pressure during ventricular systole. This is the consequence of a descent of the mitral valve anulus due to shortening of the left ventricle⁹ and is also a result of atrial relaxation in patients with sinus rhythm. In early diastole, pressure in the left atrium is reduced owing to atrial emptying, creating the mitral E wave. Therefore, the resulting diastolic forward flow in the pulmonary veins reflects the transmitral flow pattern (Figure 4). Flow from the pulmonary veins passes through the left atrium into the left ventricle, with the left atrium acting as an open conduit.⁹ Mitral valve A-wave and pulmonary venous reverse-wave flows occur in late diastole and result from atrial contraction.

With PEEP, we observed a reduction of the systolic and diastolic waves; however, the decrease of the systolic wave was less than that in the diastolic wave. This appears to be due to a preserved suction effect promoted by the descending mitral valve anulus in systole. Both pulmonary venous diastolic and mitral E waves decreased to a similar extent. Mitral E flow is dependent on the driv-

ing pressure across the mitral valve, which is determined by left atrial pressure and ventricular relaxation and compliance. Pulmonary venous diastolic flow closely follows mitral E flow. The reduction of these flows might therefore result from reduced left atrial pressure or impaired ventricular relaxation.

Mitral A and pulmonary venous reverse waves were better preserved. Atrial contraction results in forward flow through the mitral valve and in reverse flow into the pulmonary veins. In case of decreasing compliance of the left ventricle, there would be a larger increase in left atrial pressure during atrial contraction. Thus, the atrial reverse flow into the pulmonary veins would be greater than the atrial forward flow through the mitral valve.¹¹ We did not observe such an increase in reverse flow, but rather a nonsignificant decrease. This finding does not support the hypothesis of a left ventricular diastolic function disturbance initiated by PEEP. Our data show reduced filling of the atrium through the pulmonary veins with PEEP, leading to a decrease in the mitral E wave. Consequently, the results of this study favor reduction in left ventricular filling pressure, and not left ventricular diastolic compliance or relaxation disturbance, as the reason for reduced cardiac output with PEEP.

The changes in mitral valve and pulmonary venous flow patterns described in this study resemble those found recently with reduced left ventricular filling pressure.¹² The question of changes in left ventricular filling pressures with PEEP has been widely debated. Cournaud et al¹ and later Qvist et al² believed impaired venous return was the reason for decreased cardiac output. Qvist et al found a reduction in transmural filling pressures. They concluded that there was no change in left ventricular function with PEEP. However, well-maintained or even increased filling pressures with PEEP together with decreased cardiac output were found later.³ It was postu-

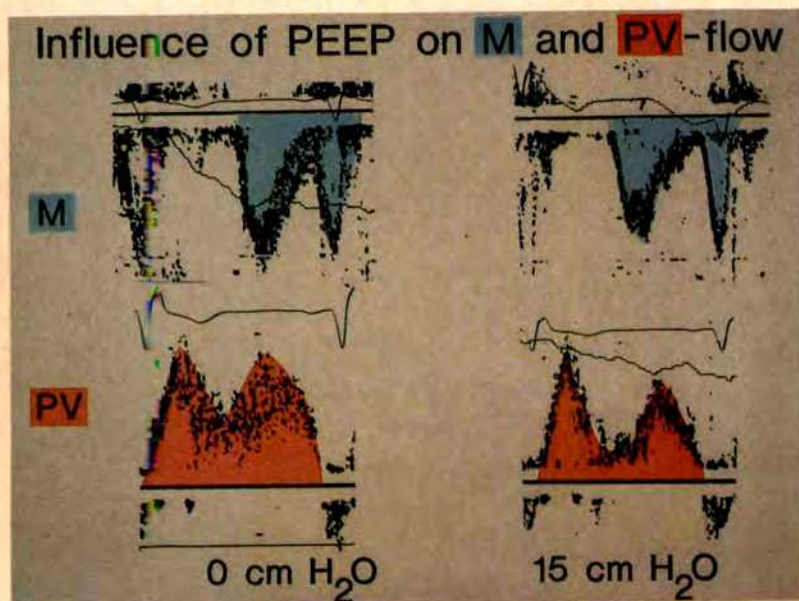


FIGURE 4. The influence of positive end-expiratory pressure (PEEP) ventilation on mitral (M) and pulmonary venous (PV) flows is shown indicating that reduction of mitral and pulmonary venous flows occurs at the same time in early diastole.

lated that left ventricular function is impaired by PEEP. These findings were questioned later using a different technique to examine juxtacardial pressure.⁵ Measuring a higher juxtacardial pressure with a lateral or posterior epicardial surface catheter resulted in lower transmural filling pressures than those reported before using esophageal, anterior pericardial and pleural pressures as indicators of juxtacardial pressure. With these lower transmural filling pressures, pressure volume curves did not show any major changes in ventricular contractility or compliance. For interpretation of hemodynamic measurements, accurate transmural pressure recordings are therefore essential. Jardin et al⁴ tried to circumvent the difficulties of transmural pressure measurements by using echocardiography, instead of this technique, to determine left ventricular function with PEEP. They found a septal shift to the left caused by right ventricular overload due to increased pulmonary artery resistance, and postulated that ventricular interdependence would alter left ventricular compliance. However, only 1 echocardiographic view was used for evaluation of the septum, and cardiac rotation with PEEP may have confounded their data. Further studies did not confirm this altered right-left ventricular volume ratio.⁶ No reduction of ejection fraction was found when using radionuclide angiography for evaluation of right and left ventricular volume.⁶ It was concluded that there was no change in left ventricular function; however, this method determines only systolic function. The ejection fraction did not change, but this investigation again was limited to systolic function. Our approach of using pulsed Doppler echocardiography for investigating complex changes occurring after induction of PEEP relinquished any intricate hemodynamic measurements. In agreement with previous studies, pulsed Doppler flow measurement provides indirect clues to left ventricular diastolic function. The combination of

mitral flow and pulmonary venous flow investigation proved especially useful in assessing loading conditions and ventricular function. This is consistent with other recent findings.¹² Combined pulsed Doppler analysis of mitral and pulmonary venous flows provides evidence that altered left ventricular filling patterns are due to reduced venous return and do not represent diastolic ventricular function impairment.

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Medical Demobilization in Wartime Russia, 1917 to 1918

Theodore L. Sourkes, PhD, and Shena Rosenblatt Sourkes, MD

The following account of Russian army demobilization in 1917, with its cardiologic overtones, is based on a story frequently told by the protagonist, the mother of one of the authors (SRS), as well as on family documents carefully preserved for more than 7 decades.

On June 13, 1917, Ginda Moissejevna Kalujna (Figure) graduated from the Women's Medical Institute of

Saint Vladimir University, Kiev, and was immediately conscripted into the Russian army as a medical officer ("ordinator" in Russian; equivalent to intern). Women serving at the warfront was an innovation introduced after the February 1917 revolution by the Kerensky government. Kalujna had enlisted under her married name as Dr. Rosenblatt, having recently wed Abraham Rosenblatt, a university student, on April 17, 1917. This young woman physician was soon elevated to the rank of captain. There was little fighting on the Allied eastern front in 1917,¹ but nevertheless, hundreds of casualties had accumulated by this time in military hospitals, and

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Dr. Ginda Moissejevna Kakujna, 1917.

the situation was further complicated by great economic disorganization, difficulties of transport, and mutinous movements among the troops against the traditional, severe disciplinary practices of the Russian army.² Supplies of food, clothing, bandages and medicine were running low. Dr. Rosenblatt would never forget the hospital wards filled with patients moaning and screaming with pain, often wishing for death. She had experienced some of this previously during her medical studies while serving as a "feeder" (doctor's assistant), from June 10, 1915, to April 1, 1916, in the No. 7 District Hospital in Kiev, the capital of the Ukraine.

Upon induction into the army, Dr. Rosenblatt was initially assigned to the 266th Infantry Regiment, serving at the military hospital in Ostrog, a town about 160 km west of Zhitomir in the Ukraine (i.e., on Russia's southwest front facing the Austro-Hungarian army). She was at once immersed in the work of attending to the ill and wounded. Later, she was assigned a post even closer to the fighting front.

Rosenblatt's superior officer was Dr. Henryk Zamenhof (1871 to 1935?), a dermatologist, one of several brothers of Ludwig L. Zamenhof. Ludwig, an ophthalmologist, had attained fame as a humanist and as the inventor of Esperanto.³ Close to the front and to the miseries engendered by the war, and facing the most serious shortages of food and medical supplies, Rosenblatt and her colleagues had to make sharp decisions in order to ease the situation. The revolution had given birth to committees in the army, and these began to act quite independently of the central government. In Ostrog, the regimental committee decided to end their part in the war by simple demobilization. The ranks were already being depleted by desertions, but for those remaining

soldiers who were mobile, the medical officers agreed to provide medical discharges. As this was to apply also to the commissioned personnel, Zamenhof, Rosenblatt and the other medical officers had to work out a plan to justify their departure from the armed service. As a result of their deliberations, they proceeded to examine their fellow officers, frequently "discovering" that they suffered from "heart ailments." That these examinations were pro forma, inspired by the need to meet the unusual situation, is clear from the fact that Zamenhof, although very hard of hearing, performed many of the auscultations and signed the discharges, including that of Ginda Rosenblatt! Their work went on apace, and on December 12, 1917, Ginda wrote her husband in Moscow that "the Medical Commission had nearly completed its work" and that she would soon be free.

This brief story relates one of the minor ways in which the war on Russia's western front was brought to an end.

On receiving her honorable discharge in 1918, Rosenblatt returned to Kiev to look for her husband. He had served in the Russian army since 1914, becoming a junior lieutenant after the February revolution. He received a leg wound in 1917 while on Russia's northwest front. After recovering, he was able to get to Moscow, and eventually to Kiev, where the couple was reunited.

After the war, Dr. Rosenblatt practiced medicine in Bessarabia, which had been taken by Romania. From 1920 to 1922, she worked in Briceni at the Municipal Hospital, and from 1923 to 1934, she lived in Lipcani, a nearby town, where she directed a clinic sponsored by OSE (an international organization providing health services to Jewish populations), and also engaged in private practice. In May 1934, she emigrated with her family to Toronto, Canada. Two years later, she fulfilled the requirements for the M.D. degree at the Faculty of Medicine, University of Toronto, but decided to devote the second part of her professional career to social work in Toronto and later Montreal. She was intellectually active till the end of her long life at age 95 years in Montreal (1891 to 1986).

Acknowledgment: We gratefully acknowledge the assistance of Professor Stephen Zamenhof, PhD, in confirming Dr. Rosenblatt's identification of her superior officer as Henryk Zamenhof (Stephen's father).

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Benjamin Franklin's *Poor Richard's Almanack* and Its Maxims on Physicians, Medicine and Nutrition

As a boy one of my favorite books was Benjamin Franklin's autobiography.* Only recently did I read his *Poor Richard's Almanack*, the most popular publication of the American colonies. This piece will present some of Poor Richard's maxims on health and its providers. But first some facts on Poor Richard's author, one of our greatest Americans and probably the first world citizen.²⁻⁵

Benjamin Franklin was born in Boston on January 6, 1706, and died in Philadelphia on April 17, 1790. He was the fifteenth of 17 children, and the youngest of 10 sons. He never remembered when he could not read. At age 8 he started school but by 10, for financial reasons, his father pulled him out to work in his shop making candles and soap. At age 12 he became a journeyman in a brother's printing business. By 16 he was writing pieces in his brother's newspaper under the name "Silence Dogood." At 17 he became a vegetarian so that he could have more money to buy books. (Years later at a fish fry, he saw little fish removed from the stomachs of the larger ones and thought, "If you eat one another, I do not see why we may not eat you. It was then easy to return to an omnivorous diet.") At 18 he left Boston for New York City, but when unable to find employment he sailed for Philadelphia where he became a journeyman printer the day after arriving in October 1723. A year later he went to London to acquire materials to set up his own printing company but he was unable to find financing. He worked in London as a printer for 18 months before returning to Philadelphia in October 1726. At age 22 he formed the *Junto*, a self-improvement and mutual aid society for ambitious young men, and it later became the American Philosophical Society. At age 23 (1728) he began his own printing business (initially with a partner) and the next year purchased the failing *Pennsylvania Gazette* which, during the next 10 years, became the most widely read newspaper in the colonies, inhabited by about 3,000,000 persons. In 1730 his son William was born out of wedlock to an unidentified mother, and later that year he formed a common-law union with Deborah Read Rogers, whose husband had run away, and to whom he was "married" for 44 years. At age 26, Franklin started

the first American subscription library, formed the first of several printer partnerships in other colonies, and wrote and published the first of the 25 annual issues of *Poor Richard's Almanack*, which ceased in 1757 when Franklin left for a near 20-year sojourn in London. At age 32 (1737) he became Postmaster of the Pennsylvania colony and at age 48, Postmaster General of North America. Another son was born in 1737 (he died 4 years later) and his daughter was born in 1743.

At age 43 (1748) Franklin, now a man of means, retired from the day-to-day activities of his printing company by bringing in a partner. For the remaining half of his life (42 years) he devoted himself primarily to scientific research, civic affairs, and statesmanship. In Philadelphia, he organized the first police force and the first fire company in the colonies, initiated the lighting and paving of streets, co-founded the first hospital (later called the University of Pennsylvania Hospital)^{6,7} and an academy (later to be the University of Pennsylvania), and he became president of the first abolition society (although at one time he owned slaves).



FIGURE 1. Benjamin Franklin at age 78 (1783) while in Paris.

*My father in 1925 also wrote a piece on Benjamin Franklin.¹ The first sentence of his article was better than mine: "Two hundred and fourteen years after Columbus discovered America and seventy before the Declaration of Independence, there was born in the bleak Boston in the early eighteenth century a boy by the name of Benjamin Franklin. . ."

Shortly after retirement from business, Franklin began his experiments on electricity. He proved that lightning was electricity, and invented the lightning rod ("Franklin's rod").^{8,9} He was recognized as the leading American scientist of that day and the authority on electricity.^{8,9} His studies made him immensely famous, a member of the important learned societies in Europe, and the best known American by Europeans. He also invented the Franklin Stove (This was the first stove—also called the Pennsylvania fireplace—that made a cold room warm and comfortable and free from smoke.¹), a rolling press for making copies of letters, an artificial hand and arm for placing books on high shelves, bifocal eyeglasses, the water-glass harmonica, and a flexible urinary catheter made of silver. His contributions to medicine were many.¹⁰⁻¹⁸ In 1759 at age 54 he received 2 honorary doctorate degrees (St. Andrews and Oxford) and thereafter he was called "Doctor Franklin."

In 1757 (age 52), Franklin was appointed agent to England from the Pennsylvania Colony (later also from 3 other colonies) and he returned to North America only once until 1775 (age 70). His wife, who refused to cross the Atlantic, died in 1774 at age 69. He was well equipped to be America's "agent" to London (or later to Paris). As Postmaster General, Franklin read most newspapers in the colonies and he had visited most post offices so he knew America well. Franklin was one of the early backers of independence for the American colonies. Upon returning from England, he headed the delegation from the Pennsylvania Colony to the Congress which wrote the Declaration of Independence (1776). Later that year he was elected Commissioner to France to seek their support for the American side during the Revolutionary War. He did not return to North America until 1785. In 1787 he was a delegate to the Constitutional Convention.¹⁹ Three years later, at age 85, he died.

In France, Franklin was regarded as a friend of humankind. John Adams said he was better known than Frederick the Great or Voltaire. His phrase *ca ira*—it will all come right in the end—became the song of the French Revolution. He was full of witticisms, jokes, memories, knowledge and keen observations, and these, with his charity and gentleness, made him a charming and available social asset. He was represented in France in busts and prints, in statuettes, on snuffboxes, on rings, and in miniatures, on handkerchiefs and dishes, and in medallions. All these images showed him as patriarchal, old and wise, and his face became as familiar as that of the moon.²

Poor Richard's Almanack, like other almanacs of the time, contained calendars and road-books with lists of places to stay and descriptions of the highways, the names of British kings and rulers of Europe, dates of eclipses, days for courts and fairs, a chronicle of "remark-

able things," prognostications about the weather, recipes, jokes, maxims and cautionary rhymes.² Peddlers carried them in their packs with needles and pins and china bowls, worsted stockings, gloves and looking glasses. They were strung on a stick and hung by the fireplace, often with records of the family written in for many years. They were sometimes paid for in wheat and potatoes, a handful of nails or a bottle of rum.

The maxims of *Poor Richard's Almanack* were not all Franklin's own. They were, he said, "the wisdom of many ages and nations," and he borrowed them freely from Dryden, Pope, La Rochefoucauld and Rabelais, changing the words, reworking them, and including popular adages.² His rule for writing, he once said, was to be "smooth, clear, and short." His sayings soon passed into everyday speech and were quoted in sermons, on title pages of pamphlets, or as mottoes in newspapers. In the twenty-fifth almanac in 1758—the last one—Franklin presented "Father Abraham's Speech" or "The Way to Wealth" composed of a string of adages from previous almanacs. Most colonists, Franklin said, were "middling people" who were obliged to work and save to prosper and survive, and the popularity of the proverbs was due to this fact. They also were immensely popular in Europe.

In 1990, 200 years after Franklin's death, Peter Baida²⁰ pointed out that Franklin was the first writer of success literature. In all his work, Franklin talked about character as the source of success, citing industry, frugality, sobriety, honesty, perseverance, loyalty and reliability. Both his autobiography and the maxims in *Poor Richard's Almanack* have exerted a considerable influence for over 200 years. We can all profit from Franklin's ideas of success, whether in business or in health. The remainder of this piece lists some of Poor Richard's comments on physicians, medical wisdom, medical advice, eating, foods, alcohol and heart:

PHYSICIANS

He's a Fool that makes his Doctor his Heir.
Beware of the young Doctor & the old Barber.
God heals, and the Doctor takes the Fees.
He's the best physician that knows the worthlessness of the most medicines.

Don't misinform your Doctor nor your Lawyer.
It is ill Jestng with the Joiner's Tools, worse with the Doctor's.

MEDICAL WISDOM

Early to bed, and early to rise, makes a Man healthy, wealthy and wise.

A good Wife & Health, is a Man's best Wealth.
A good Man is seldom uneasy, an ill one never easie.
The Tongue is ever turning to the aching Tooth.
An ill Wound, but not an ill Name, may be healed.
Love, Cough, & a Smoke, can't well be hid.

Changing Countries or Beds, cures neither a bad Manager, nor a Fever.

Pride and the Gout, are seldom cur'd throughout.

We are not so sensible of the greatest Health as of the least Sickness.

If thou dost ill, the joy fades, not the pains; If well, the pain doth fade, the joy remains.

Pain wastes the Body, Pleasures the Understanding.

A long Life may not be good enough, but a good Life is long enough.

Watch the disease in time: For when, within The dropsy rages, and extends the skin, In vain for helebore the patient cries, And sees the doctor, but too late is wise: Too late for cure, he proffers half his wealth; Ten thousand doctors cannot give him health.

Death takes no bribes.

MEDICAL ADVICE

Would you live with ease, Do what you ought, and not what you please.

Keep your mouth wet, feet dry.

Hot things, sharp things, sweet things, cold things All rot the teeth, and make them look like old things.

Be temperate in wine, in eating, girls, & sloth; Or the Gout will seize you and plague you both.

Be not sick too late, nor well too soon.

He that can take rest is greater than he that can take cities.

Don't go to the doctor with every distemper, nor to the lawyer with every quarrel, nor to the pot for every thirst.

To Friend, Lawyer, Doctor, tell plain your whole Case. . . .

Time is an herb that cures all Diseases.

EATING

Eat to live, and not live to eat.

To lengthen thy Life, lessen thy Meals.

Three good meals a day is bad living.

Eat few Suppers, and you'll need few Medicines.

Dine with little, sup with less: Do better still; sleep superless.

Sleep without Supping, and you'll rise without owing for it.

He that lives carnally, won't live eternally.

Many dishes many diseases, Many medicines few cures.

I saw few die of Hunger, of Eating 100000.

A full Belly is the Mother of all Evil.

A full Belly makes a dull Brain: The Muses starve in a Cook's Shop.

Hold your Council before Dinner; the full Belly hates Thinking as well as Acting.

If it were not for the Belly, the Back might wear Gold.

No wonder Tom grows fat, th' unwiedly Sinner, Makes his whole Life but one continual Dinner.

9 Men in 10 are suicides.

He that never eats too much, will never be lazy.

Hunger is the best Pickle.

Too much plenty makes Mouth dainty.

Where there is Hunger, Law is not regarded; and where Law is not regarded, there will be Hunger.

He that would travel much, should eat little.

Fools make feasts and wise men eat them.

A fat kitchen, a lean Will.

Give me yesterday's Bread, this Day's Flesh, and last Year's Cyder.

Many a Meal is lost for want of meat.

Eat to please thyself, but dress to please others.

How happy is he, who can satisfy his hunger with any food, quench his thirst with any drink, please his ear with any musick, delight his eye with any painting, any sculpture, any architecture, and divert his mind with any book or any company! How many mortifications must he suffer, that cannot bear anything but beauty, order, elegance & perfection! *Your man of taste, is nothing but a man of distaste.*

On the 18th of this month, anno 1546 died that famous reformer, LUTHER: who struck the great blow to papal tyranny in Europe. He was remarkably temperate in meat and drink, sometimes fasting four days together; and at other times, for many days eating only a little bread and a herring. Cicero says, There was never any great man who was not an industrious man; to which may, perhaps, be added, There was never any industrious man who was not a temperate man: For intemperance in diet, abates the vigour and dulls the action both of the mind and body.

. . . eat for Necessity, not Pleasure, for Lust knows not where Necessity ends. . . .

If thou art dull and heavy after Meat, it's a sign thou hast exceeded the due Measure; for Meat and Drink ought to refresh the Body, and make it cheerful, and not to dull and oppress it. . . .

Keep out of the Sight of Feasts and Banquets as much as may be; for 'tis more difficult to refrain good Cheer, when it's present, than from the Desire of it when it is away. . . .

If a Man casually exceeds, let him fast the next Meal, and all may be well again, provided it be not too often done; as if he exceed at Dinner, let him refrain a Supper, . . .

A temperate Diet frees from Diseases; such are seldom ill, but if they are surprised with Sickness, they bear it better, and recover sooner . . .

Use now and then a little Exercise a quarter of an Hour before Meals, as to swing a Weight, or swing your Arms about with a small Weight in each Hand; to leap, or the like, for that stirs the Muscles of the Breast.

A temperate Diet arms the body against all external Accidents; so that they are not so easily hurt by Heat, Cold or Labour; if they at any time should be prejudiced, they are more easily cured, either of Wounds, Dislocations or Bruises.

But when malignant Fevers are rife in the Country or City where thou dwelst, 'tis adviseable to eat and drink more freely, by Way of Prevention; for those are Diseases that are not caused by Repletion, and seldom attack Full-feeders. . . .

FOODS

Much Virtue in Herbs, little in Men.
When you taste Honey, remember Gall.
Cheese and salt meat, should be sparingly eat.
The misers cheese is wholesomest.
After Fish, Milk do not wish.
An Egg to day is better than a Hen to-morrow.
Pray don't burn my House to roast your Eggs.
Onions can make ev'n Heirs and Widows weep.

ALCOHOL

There's more old Drunkards than old Doctors.
Nothing more like a Fool, than a drunken Man.
Life with Fools consists in Drinking . . .
He that drinks fast, pays slow.
Poor Dick, eats like a well man, and drinks like a sick.
Against Diseases here, the strongest Fence, Is the defensive Virtue, Abstinence.
He that drinks his Cyder alone, let him catch his Horse alone.
He that spills the Rum, loses that only; He that drinks it, often loses both that and himself.
When the Wine enters, out goes the Truth.
Take counsel in wine, but resolve afterwards in water.
Drink Water, Put the Money in your Pocket, and leave the Dry-bellyach in the Punchbowl.

HEART

Light purse heavy heart.
The heart of a fool is in his mouth, but the mouth of a wise man is in his heart.

When Man and Woman die, as Poets sung, His Heart's the last part moves, her last, the tongue.

Great Beauty, great strength, & great Riches, are really & truly of no great Use; a right Heart exceeds all.



William Clifford Roberts, MD
Editor in Chief

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**SUMMARY (FOR FULL PRESCRIBING
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INDICATIONS AND USAGE

Hypertension: Tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris: Tablets are indicated in the long-term treatment of angina pectoris.

Contraindications

Myocardial Infarction: Tablets and capsules are contraindicated in the treatment of patients with a recent myocardial infarction. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically stable. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically unstable. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically unstable.

Warnings

Angina Pectoris: Tablets are contraindicated in the treatment of patients with a recent myocardial infarction. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically stable. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically unstable.

Precautions

Myocardial Infarction: Tablets and capsules are contraindicated in the treatment of patients with a recent myocardial infarction. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically stable. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically unstable.

Adverse Reactions

Angina Pectoris: Tablets are contraindicated in the treatment of patients with a recent myocardial infarction. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically stable. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically unstable.

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Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute, a beta₂-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses (e.g., 25 mg twice daily, instead of larger doses two times daily, to the higher plasma levels associated with the longer half-life). (See DOSAGE AND ADMINISTRATION.)

Preoperative Evaluation: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Impaired ability of the heart to respond to reflex adrenergic stimulation may augment the risks of general anesthesia and surgical procedures.

Other Beta Blockers: Like other beta blockers, Lopressor is a competitive inhibitor of adrenergic receptors, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is used. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and weakness may not be significantly affected.

Toxicosis: Beta-adrenergic blockade may mask certain signs (e.g., tachycardia) of hyperthyroidism. Patients with developing thyrotoxicosis should be managed cautiously to avoid abrupt withdrawal of beta blockade, which may precipitate a thyroid storm.

Contraindications

Myocardial Infarction: Tablets and capsules are contraindicated in the treatment of patients with a recent myocardial infarction. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically stable. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically unstable.

Angina Pectoris: Tablets are contraindicated in the treatment of patients with a recent myocardial infarction. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically stable. Tablets are contraindicated in the treatment of patients with a recent myocardial infarction who are hemodynamically unstable.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first-, second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure \leq 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta₂-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta₂ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta₂ agonists may produce serious cardiac arrhythmias.

PRECAUTIONS

General

Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Risk of Anaphylactic Reaction: While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, arterial insufficiency, usually of the Raynaud type; palpitant congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction

Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the CLINICAL PHARMACOLOGY section, the following adverse reactions were reported:

	Lopressor	Placebo
Hypotension (systolic BP < 90 mmHg)	27.4%	23%
Bradycardia (heart rate < 40 beats/min)	15.9%	6%
Second- or third-degree heart block	4.7%	4%
First-degree heart block (P-R \geq 0.26 sec)	5.3%	1%
Heart failure	27.5%	29%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to cataplexy; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

Several cases of overdosage have been reported, some leading to death.

Oral LD₅₀'s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms

Potential signs and symptoms associated with overdosage of Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see WARNINGS, Myocardial Infarction).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed.

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levaterenol or dopamine.

Bronchospasm: A beta₂-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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Please consult Brief Summary of Prescribing Information on following page.

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